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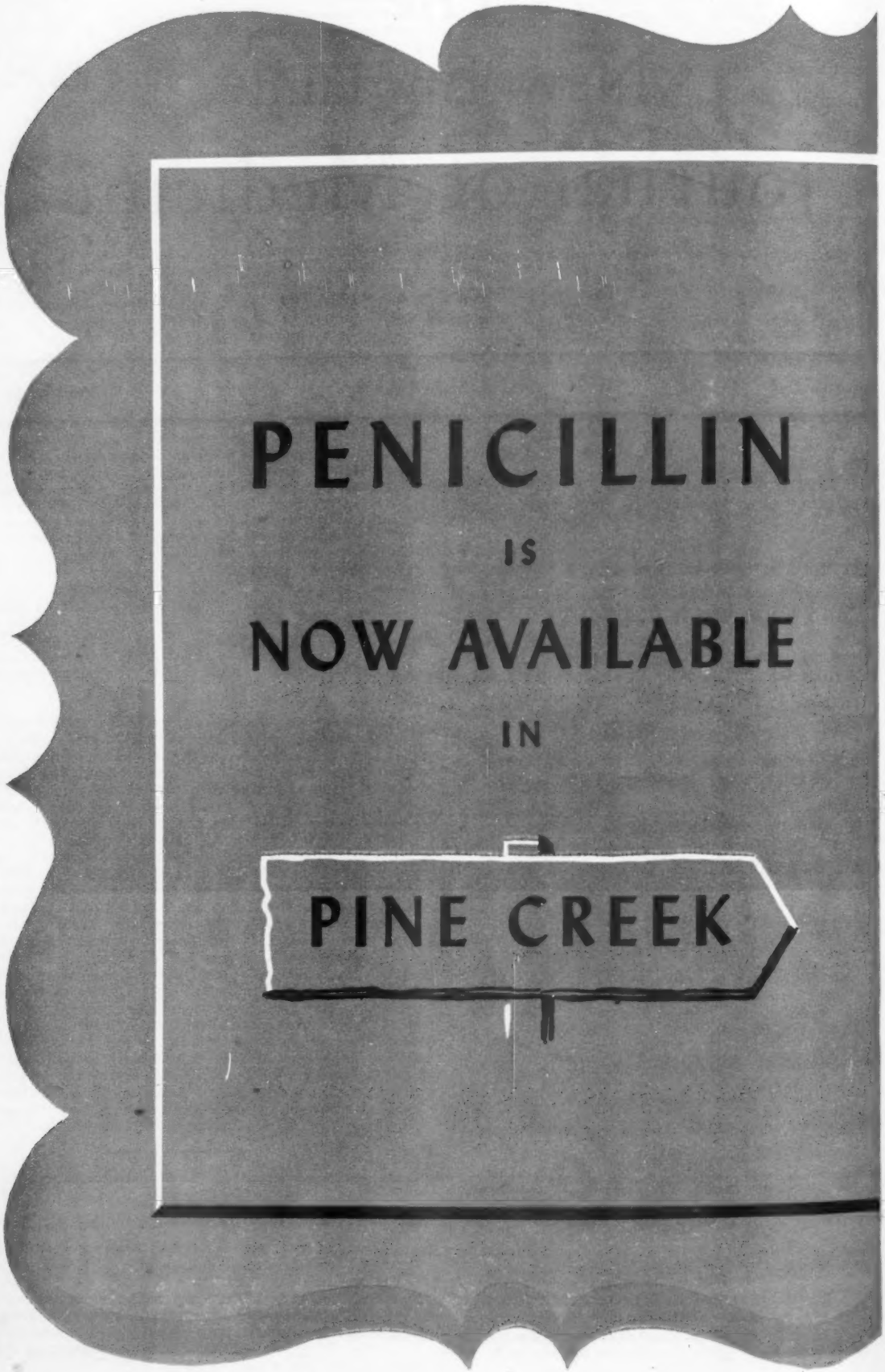
PENICILLIN
IS
NOW AVAILABLE
IN
PINE CREEK

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Volume 232 APRIL 5, 1945 Number 14

PAPAVERINE IN THE TREATMENT OF CORONARY-ARTERY DISEASE*

WILLIAM GRAY, M.D.,† JOSEPH E. F. RISEMAN, M.D.,‡ AND SAMUEL STEARNS, M.D.§

BOSTON

PAPAVERINE, an opium derivative frequently used to combat vascular spasm, was first advocated for the treatment of angina pectoris in 1913 by Pal[1]; no data were presented, however. Three years later, Macht[2] reported temporary relief of angina pectoris in 3 patients following injection of 40 mg. of papaverine. In 1923, Pal[3] described prompt but transient relief of angina pectoris after the injection of 20 to 30 mg. of papaverine intravenously in an eighteen-year-old patient with aortic stenosis and insufficiency; subcutaneous injections of larger doses were not so effective. In 1921, Boehm[4] reported marked success in treating patients with angina pectoris with 30 mg. of papaverine in a mixture with camphor, given three times daily by mouth. In 1933, Evans and Hoyle[5] reported that their studies on 31 patients offered no convincing evidence of the value of orally adminjstered papaverine over other drugs tested. More recently, interest has been stimulated by the work of Elek and Katz,[6] 12 of whose 17 patients showed definite improvement when given papaverine by mouth in doses of 100 mg. three times daily. Definite improvement was defined as a reduction of at least 25 per cent in the number of attacks, of 50 per cent in the duration of attacks and of 50 per cent in the number of nitroglycerin tablets used, or an increase in the distance that the patient could walk without pain. These authors stressed the importance of using much larger doses of papaverine than had previously been advocated.

All these investigators relied on clinical evaluation of the efficacy of therapy. It has repeatedly been shown that such methods fail to differentiate the effects of inert and active therapy,[5–12] so that objective studies are desirable. Such studies carried out in this laboratory between 1935 and 1937 showed no change in the standardized exercise-tolerance test thirty minutes after the intravenous injection of 30 mg. of papaverine in 4 cases, or in a fifth patient who received this dose orally three times a day.[13] All these patients had shown beneficial responses to other drugs. The purpose of this paper is to present the results of additional objective studies on the use of papaverine in the treatment of coronary-artery disease with the larger doses recommended by Elek and Katz.[6]

MATERIALS AND METHODS

The effect of papaverine in angina pectoris was studied in 13 patients who made regular weekly visits to the Angina Clinic of the Beth Israel Hospital. These patients varied in age from forty-six to seventy-two years; 11 were men. All had had angina pectoris for six months to fifteen years, and 6 had a history of myocardial infarction in the past. Nine patients had been followed in the clinic for four to ten years, and the other 4 were observed for one to nine months. The ability of these patients to respond to other types of therapy usually advocated for angina pectoris was known and was reevaluated at frequent intervals during the period of study. Five showed a markedly beneficial response to nitroglycerin and other therapy and were classified in accordance with the method previously described[10] as Group 1 patients. Six showed a moderate response to these drugs and were called Group 2 patients. The remaining 2 showed little or no response to any of the usual forms of therapy and were termed Group 3 patients.

On each visit the patient was questioned carefully concerning the number of attacks of angina pectoris experienced since the last visit, the number of tablets of nitroglycerin used and the amount of physical and emotional strain sustained during the week. The patient's evaluation of the therapy was recorded, as was any unusual increase in ability to walk without production of angina. On each visit the amount of work necessary to induce angina was measured by the standardized exercise-tolerance test, carried out in a cold room, as previously described.[14] Many determinations of this tolerance

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were made while the patient was taking inert medication or placebos. The usual upper limit of tolerance while the patient was taking inactive medication was selected as a base line for comparison (Fig. 1).

On each visit the patient was given a supply of medication to be taken four times a day for at least one week. The results with papaverine hydrochloride* (100 or 200 mg.) were compared with those with other medications, including placebos.

The effect of papaverine hydrochloride given intravenously was determined in the following manner while the patients were taking inert medication (enteric-coated lactose). A solution containing 65 to 100 mg. of papaverine hydrochloride, usually diluted to 10 cc. with physiologic saline solution, was given intravenously, and the standardized exercise tolerance was measured at intervals varying from five to ninety minutes after injection. Each injection required about two minutes. Only one test was carried out on any given visit. The different doses used at varying time intervals served to check the results.

Electrocardiographic studies, according to the method previously described,[12, 15] were carried out in 2 patients who had shown a beneficial response to intravenously administered papaverine. In these studies a control precordial tracing (Lead 4R) was taken with the patient standing at rest and also for fifteen seconds *immediately* after the cessation of exercise that induced an attack of angina. At a subsequent visit, identical studies were repeated after the administration of papaverine intravenously. To obtain such tracings, it was necessary for the patient to exercise with the electrodes in place and with the electrocardiograph running. In all cases the degree of RST deviation was measured as the average of ten consecutive complexes.

Clinical observations of the effect of 65 mg. of papaverine hydrochloride given intravenously for the relief of pain in 8 patients with acute myocardial infarction and in 3 with acute coronary failure were also made on the wards of the hospital. These patients varied in age from forty-nine to seventy-five years; 9 were men. In most cases, the solution of papaverine used was not diluted with physiologic saline solution.

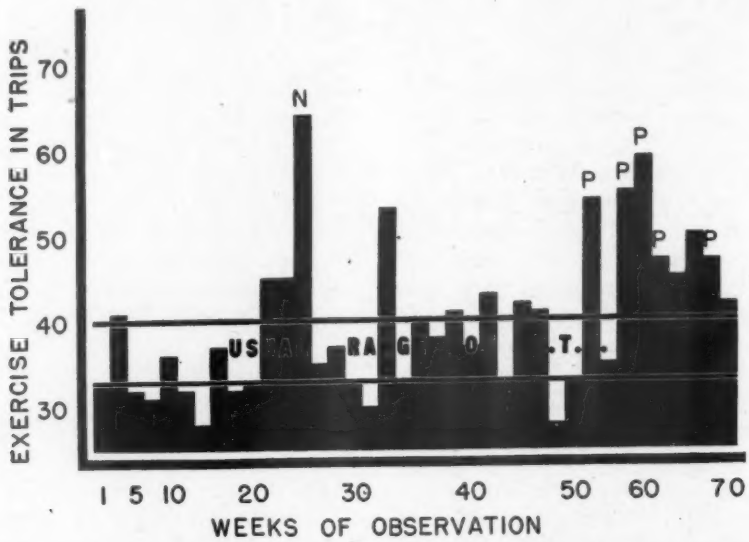

FIGURE 1. *Studies of Standard Exercise Tolerance in Case 10 during a Period of 68 Weeks.*

N indicates standard exercise tolerance after nitroglycerin, and P, after papaverine given intravenously. The medication during the period was as follows, according to weeks: 1-11, enteric-coated lactose; 12, 30 cc. whisky four times a day; 13-15, none; 16, 100 mg. Syntropan four times a day; 17-19, none; 20-23, enteric-coated lactose; 24-25, 0.3 gm. sodium bicarbonate four times a day (25, test, 2 min. after 0.3 mg. nitroglycerin); 26-33, 0.13 gm. Pavatrine four times a day; 34, 0.2 gm. Theopropanol four times a day; 35-36, 0.3 gm. sodium bicarbonate four times a day; 37, 200 mg. papaverine hydrochloride orally four times a day; 38, 100 mg. Syntropan four times a day; 39, 30 mg. Prostigmin four times a day; 40, 1 gm. potassium chloride four times a day; 41, 2 gm. potassium chloride four times a day; 42-43, 0.3 gm. sodium bicarbonate four times a day; 44, 200 mg. ascorbic acid four times a day; 45-46, none; 47, 1.5 mg. physostigmin salicylate four times a day; 48-61, enteric-coated lactose (55, test, 15 min. after 65 mg. papaverine hydrochloride intravenously; 59, test, 5 min. after same dose; 60, test, 10 min. after same dose; 61, test, 30 min. after same dose); 62-64, none; 65-68, enteric-coated lactose (65, test, 10 min. after 100 mg. papaverine hydrochloride intravenously; 67, test, 15 min. after 100 mg. Octin subcutaneously; 68, test, 60 min. after 65 mg. papaverine hydrochloride intravenously).

RESULTS

Oral Administration in Angina Pectoris

Clinical evaluation. The effect of papaverine hydrochloride given by mouth was tested in 11 patients. There were twenty trial periods, in which 10 patients received 100 mg. and 10 received 200 mg.

*The papaverine hydrochloride used in this study was furnished through the courtesy of Eli Lilly and Company, Indianapolis, Indiana.

four times a day for one week. Toxic symptoms developed in 5 patients. One (Case 13) was unable to take more than a single dose of the drug on each of two trials because of severe nausea. This patient had previously developed severe nausea necessitating cessation of therapy while taking Dilaudid (3 mg.) or morphine sulfate (8 mg.) by mouth. Two patients were unable to take doses of 200 mg. because of severe nausea, accompanied in 1 case by abdominal cramps, but were able to tolerate doses of 100 mg. Two patients developed slight nausea after 200-mg. but not after 100-mg. doses.

No demonstrable clinical improvement occurred in any of the 10 patients able to tolerate papaverine by mouth (Table 1). Only 1 patient (Case 1) stated that he believed papaverine to be helpful, but he actually had more than the usual number of attacks while taking the drug. None of the other patients made any favorable comments about the action of the drug. In 5 cases, the number of attacks of angina pectoris was the same as that while on placebos; in 4, the number of attacks was almost double the control value; in 1, no attacks were experienced while on papaverine but the patient had had the same experience during many weeks on a placebo.

Objective studies. In each of the sixteen determinations made on the 10 patients studied, the standardized exercise tolerance was equal or within −16 per cent of the maximum amount of work that could be done when taking inert medication or placebos (Table 2). The results with a dose of 200 mg. were no better than those with 100 mg.

TABLE 1. *Clinical Evaluation of Papaverine Hydrochloride Given Orally.*

Case No.	Placebo Therapy	Papaverine Therapy				
	Frequency of pain*	Frequency of pain*		Toxic effect		Therapeutic effect‡
		100-mg. dose	*200-mg. dose*	*100-mg. dose*	*200-mg. dose*	
Group 1:						
1	3–4	4–5	6	None	None	Beneficial
2	6–8	12–15	—†	None	Severe nausea	Not beneficial
3	14–15	30	21	None	Slight nausea	Not beneficial
4	1–2	3		None		Not beneficial
Group 2:						
6	0–3	2	2	None	None	Not beneficial
7	3–5	3	—†	Slight nausea	Severe nausea Abdominal cramps	Not beneficial
8	4–6	6	7	None	None	Not beneficial
9	0–2	1	0	None	Slight nausea	Not beneficial
10	2–3		2		None	Not beneficial
Group 3:						
11	6–10	12–15	12–15	None	None	Not beneficial
13	4–5	—†	—†	Severe nausea	Severe nausea	Not beneficial

*Average number of attacks (or number of nitroglycerin tablets) per week.
†Patient unable to tolerate this dose.
‡According to patient.

Intravenous Administration in Angina Pectoris

Clinical evaluation. Twelve patients were studied and a total of fifty-two injections were given. Typical circulation-time reactions, as described by Elek and Solarz,[16] occurred in fifteen to twenty-five seconds after the injection was begun. These consisted of hyperpnea, flushing of the face with a feeling of warmth throughout the body, slight dizziness, a sensation of throbbing in the temples and slight tachycardia. In most cases these were not disturbing to the patients, but in 3 cases they were so severe that the patient refused to allow additional injections of the drug after two trials. Dilution with 10 cc. of physiologic saline solution permitted slower injection and decreased the severity of these reactions but did not eliminate them. In patients experiencing severe circulation-time reactions, transient nausea and sweating were frequent. Drowsiness lasting for about an hour followed each injection in 1 patient, but this was not severe enough to necessitate stopping injections.

One patient received papaverine hydrochloride intravenously on two occasions during attacks of angina pectoris. On one of these the attack disappeared as the injection was continued; on the other the pain became worse and more prolonged. There was no appreciable difference in the severity or frequency of toxic effects following doses of 65 or 100 mg.

TABLE 2. *Objective Evaluation (Standardized Exercise Tolerance) of Papaverine Hydrochloride Given Orally.*

Case No.	Placebo Therapy	Papaverine Therapy	
		100-mg. dose	200-mg. dose
	trips	*trips*	*trips*
Group 1:			
1	18–24	22	24
2	22–26	26	—*
3	43–52	42	43
4	24–26	22	
Group 2:			
6	20–24	24	23
7	18–22	20	—*
8	28–36	34	32
9	25–32	31	28
10	33–40		40
Group 3:			
11	22–28	24	24
13	24–30	—*	—*

*Patient unable to tolerate this dose.

Objective studies. Six of the 12 patients studied showed no significant increase in exercise tolerance following intravenous injection of papaverine (Fig. 2 and Table 3). In the remaining 6 cases, increases of 25 to 57 per cent were noted (Fig. 3); these comprised 3 of 4 Group 1 and 3 of 6 Group 2 patients. The maximum increase in exercise tolerance oc-

curred in five to fifteen minutes after injection, with a slight effect persisting as long as sixty to ninety minutes. There was no appreciable difference in results following doses of 65 or 100 mg.

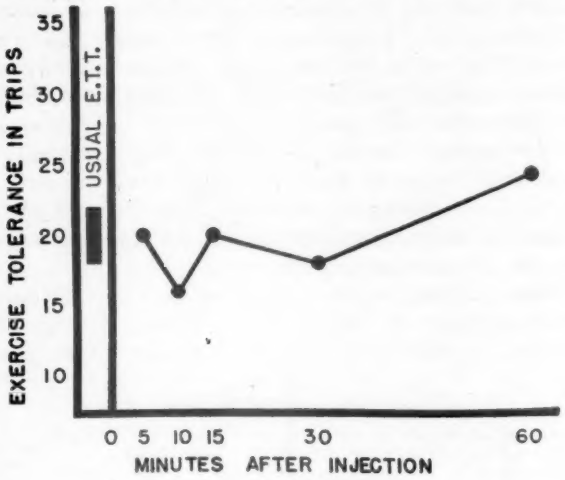

FIGURE 2. *Case 7.*

The chart shows the absence of increase in standardized exercise tolerance following the intravenous injection of papaverine hydrochloride.

Electrocardiographic studies were carried out in 2 patients who had shown a response to intravenous papaverine. In one, the RST segment, after twenty-six trips that produced an attack of angina, was depressed 3.0 mm. After the injection of 65 mg. of papaverine hydrochloride intravenously, the same amount of exercise failed to induce angina, and the RST depression was 2.1 mm. five minutes after injection, 2.5 mm. ten minutes after injection and 2.0 mm. fifteen minutes after injection. Two minutes after the sublingual administration of 0.7 mg. of nitroglycerin, the RST depression was 1.2 mm. (Fig. 4). In the second patient, the RST depression during angina induced by thirty-four trips was 1.6 mm., and fifteen minutes after the injection of papaverine the same amount of work failed to induce angina and the RST depression was 2.0 mm.

Intravenous Administration in Acute Myocardial Infarction or Coronary Failure

Mild undesirable side effects were seen in 5 of the 11 cases studied. These consisted of slight dizziness in 1 case, nausea and vomiting in 1, drowsiness in 1 and moderately severe circulation-time reactions in 2. In general, even when the papaverine was not diluted with saline solution, the toxic effects in this group were not so severe as in the ambulatory less acutely ill patients with angina pectoris.

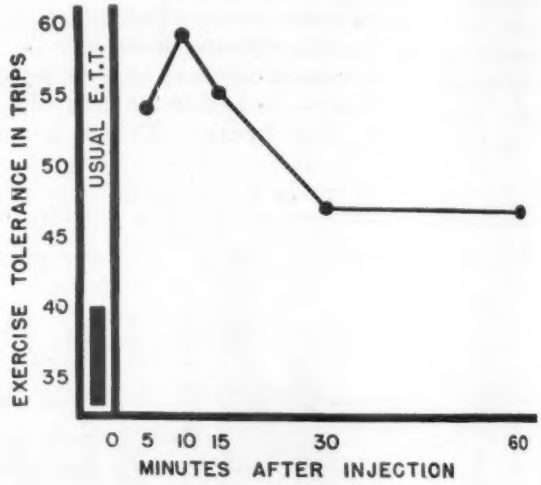

FIGURE 3. *Case 10.*

The chart shows an increase in standardized exercise tolerance following the intravenous injection of papaverine hydrochloride.

Sixty-five milligrams of papaverine hydrochloride given intravenously was followed by relief of pain in 5 of 8 cases of acute myocardial infarction and in 1 of 3 cases of coronary failure within forty

TABLE 3. *Objective Evaluation (Standardized Exercise Tolerance) of Intravenous Injection of Papaverine Hydrochloride.*

Case No.	Placebo Therapy	Papaverine Therapy							
			Interval after injection						
		dose	5 min.	10 min.	15 min.	20 min.	30 min.	45 min.	60 min.	90 min.
	trips	*mg.*	*trips*	*trips*	*trips*	*trips*	*trips*	*trips*	*trips*	*trips*
Group 1:										
1	18–24	65	22+	31	28	—	30	—	24	—
2	22–26	65	35	35	33	—	33	31	31	30
		100	—	34	—	—	—	—	—	—
3	43–52	65	49	35	38	—	51	—	35	—
5	24–28	65	—	44+	—	—	—	—	—	—
Group 2:										
6	20–24	65	22	22	20	—	—	—	—	—
		100	—	—	23	—	—	—	—	—
7	18–22	65	20	16	20	—	18	—	24	—
		100	—	20	22	—	—	—	—	—
8	28–36	65	38	—	32	—	—	—	—	—
9	25–32	65	36+	34+	46+	42+	—	38+	31	—
		100	—	32+	—	—	—	—	—	—
10	33–40	65	55	59	54	—	47	—	47	—
		100	—	45	—	—	—	—	—	—
12	14–19	65	—	24+	—	—	—	—	—	—
Group 3:										
11	22–28	65	20	—	—	30	—	—	—	—
13	24–30	33	26	—	—	—	—	—	—	—
		65	21	—	—	—	—	—	—	—

+Indicates that angina was not produced. Exercise terminated because of fatigue or leg cramps.

seconds to two minutes of injection. In most cases, relief of pain occurred at about the same time as the circulation-time reaction. In 2 cases of myocardial infarction in which the previous administration of morphine and Dilaudid had been unsuccessful in relieving severe pain, the complete relief following injection of papaverine was dramatic. In a third case of myocardial infarction with severe pain, two 65-mg. injections of papaverine hydrochloride at ten-minute intervals afforded no relief, whereas morphine sulfate intravenously was beneficial. In 1 patient with coronary failure, the precordial pain became more severe during the injection of papaverine.

Discussion

It is evident from these studies that papaverine hydrochloride given by mouth, in doses of 33, 100 or 200 mg. four times daily for one week, is of little value in the clinical treatment of angina pectoris. This is demonstrated by the fact that none of the 11 patients studied were able to perform more work under standardized conditions after taking papaverine than they could do without the drug, and by the lack of significant clinical improvement. Larger doses are impractical because they cause gastric distress.

These results are not in accord with those of Elek and Katz,[6] who first advised larger doses than had previously been used. The number of patients in the present series is admittedly small, but 9 of the 11 patients were able to do more work after effective drugs such as nitroglycerin. The patients received the drug for only one week at a time, for experience indicates that the response to vasodilator drugs occurs following each, even the first, dose. The effect of therapy over longer intervals is difficult to evaluate because periods of comfort, unrelated to therapy, are likely to be included. Another, probably more important, reason for the difference in results is that Elek and Katz relied on the history for evaluation of the effect. This method has been demonstrated to be of limited value.[5, 7–9, 11, 12] The patients in the present series only rarely believed that papaverine was of benefit. This was presumably because their long experience with the method of study had led them to observe the clinical course more critically than did patients studied for the first time.

The present observations of the effect of papaverine hydrochloride administered intravenously are in accord with those of Macht,[2] Pal[3] and Elek and Katz,[6] which showed that this drug has a definite but temporary effect on the heart. In the present studies, a vasodilator effect was demonstrated by an increased ability to work in 6 of 12 patients and by less marked electrocardiographic changes following exercise. This action is of little value in the treatment of ambulatory patients with angina pectoris because repeated intravenous therapy is impractical and because the beneficial results are transient, infrequent and not so great as with other available therapy.

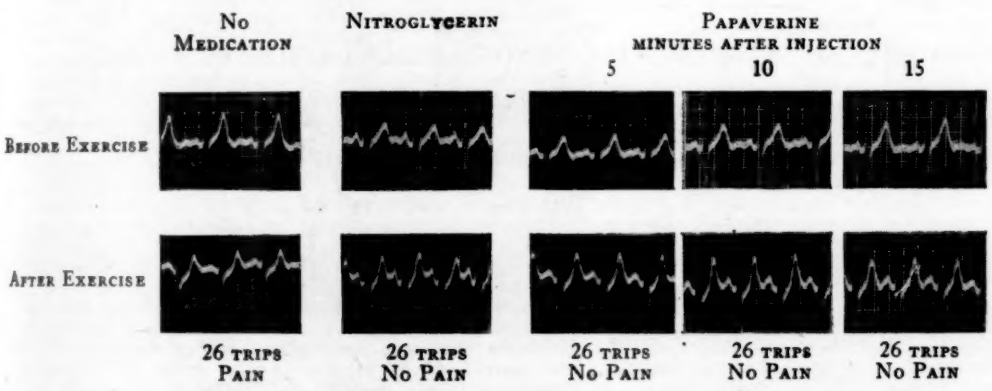

Figure 4. *Case 2.*

Papaverine hydrochloride given intravenously for treatment of the precordial pain of coronary occlusion or coronary failure appears to be of value even though the beneficial action is only temporary. Final decision on its use in such conditions must await further experience, for not all patients are benefited, and the administration of drugs intravenously to such patients is not without some danger.

Summary and Conclusions

Papaverine hydrochloride appears to have a definite but limited and temporary vasodilator action in patients with coronary-artery disease.

The administration of this drug intravenously enabled half the patients with angina pectoris to do more work than was possible otherwise and decreased the electrocardiographic changes following exercise. This effect reached its maximum in five to fifteen minutes after injection and was negligible after about sixty minutes. This method of therapy,

however, is of little value in the clinical treatment of patients with angina pectoris.

The oral administration of papaverine hydrochloride in doses of 33, 100 or 200 mg. to ambulatory patients did not improve their ability to exercise, and does not appear to be of practical value in the treatment of angina pectoris.

Studies in a small group of patients suggest that the administration of papaverine hydrochloride intravenously in doses of 65 or 100 mg. is of considerable value in treating the pain of coronary occlusion or coronary failure.

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PLETHORA OF THE INTRACRANIAL VENOUS CIRCULATION IN A CASE OF POLYCYTHEMIA*

Pathologic Physiology and Diagnostic Considerations

JULIUS LOMAN, M.D.,† AND WILLIAM DAMESHEK, M.D.‡

BOSTON

IN POLYCYTHEMIA vera, symptoms referable to the head greatly outrank in incidence those relating to any other bodily system.[1] Actual cerebral vascular lesions are, furthermore, not infrequent. These include arterial or venous thromboses and hemorrhage, which is either intracerebral or subarachnoid in location. The development of extreme headache, amblyopia, papilledema and increased intracranial pressure in a case of well-marked secondary polycythemia led to studies that are of interest from the standpoint of intracranial dynamics, and to the conclusion that extreme plethora may result in changes indistinguishable from those occurring in other types of increased intracranial pressure.

Case Report

A. F. L., a 41-year-old male, was referred to the Joseph H. Pratt Diagnostic Hospital from the Boston Dispensary on October 2, 1942. He complained chiefly of severe headache and failing vision of 1 year's duration. Since the age of 10, he had suffered from severe perennial asthma, with frequent attacks lasting as long as 12 hours. On several occasions he had had small hemoptyses, which were usually associated with a dull aching sensation in the chest. In recent years, he had been completely incapacitated because of increasing exertional dyspnea. For the past year the vision had become increasingly blurred, and was frequently associated with scintillating scotomas and small black spots before the eyes. Beginning about a month before admission, the patient developed a continuous and severe occipital headache that was unassociated with nausea or vomiting and unrelieved by aspirin. For 2 weeks there had been occasional staggering with walking.

Examination disclosed an extremely cyanotic man, lying flat in bed without much respiratory distress. The eyeballs were somewhat prominent. The pupils were round and equal and somewhat dilated, and reacted poorly to light and accommodation. The vessels of the scleras were deeply injected. The conjunctivas were deep purple. The retinal vessels, particularly the veins, were greatly distended. Both optic disks showed pronounced choking, particularly marked over the nasal halves. Numerous pinpoint hemorrhages were scattered throughout both fundi.

The anteroposterior diameter of the thorax was greatly increased, with very limited excursion, respirations being almost entirely abdominal. The percussion note was hyperresonant throughout, with complete absence of absolute cardiac dullness. Numerous sonorous and sibilant rhonchi and occasional crepitant inspiratory rales were heard. The heart sounds were distant and heard only over the xiphoid cartilage. There were no murmurs. The blood pressure was 135/90. There was marked distention of the veins in the upper extremities, and large varicosities were present bilaterally. The fingers were not definitely clubbed. Neurologic examination showed intact cranial nerves, active and equal reflexes of the arms, and knee jerks that were equal but barely obtainable on reinforcement. Ankle jerks were equal and active. There was an equivocal Babinski sign on the right and definite Babinski and Chaddock signs on the left. There was no ankle clonus.

The urine showed a +++ test for albumin and a few hyaline and fine granular casts in the sediment. The specific gravity was 1.018, and there was good concentration with a modified Fishberg test. The blood findings were as follows: hemoglobin, 136 to 142 per cent (21.1 to 22.0 gm.); reticulocytes, 0.3 per cent; red-cell count, 8,100,000 to 9,000,000; white-cell count, 6500 and 7400, with 69 per cent polymorphonuclear leukocytes, 14 per cent lymphocytes, 10 per cent

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monocytes and 7 per cent eosinophils; platelet count, 562,000 and 585,000; hematocrit, 80 per cent. The blood sedimentation rate was 0 mm. in 1 hour, and the same in 2 hours. Blood Hinton and Wassermann reactions were negative.

Spinal-fluid examination on October 3 showed a cell count of 2, both lymphocytes, a negative globulin test and a total protein of 34 mg. per 100 cc. Davies–Hinton and Wassermann reactions were negative. The initial pressure was equivalent to 380 mm. of water; homolateral and contralateral compression over the internal jugular veins resulted in normal responses.

The heart, which was in a transverse position by x-ray, showed probable right-ventricular hypertrophy. There was definite enlargement of the pulmonary conus and possible enlargement of the right pulmonary artery. The roentgenologist's impression was severe emphysema with bleb formation, moderate pulmonary fibrosis and probable cor pulmonale. There was no evidence of pulmonary endarteritis.

The electrocardiogram showed right-axis deviation consistent with chronic cor pulmonale.

Because of the finding of the greatly increased cerebrospinal-fluid pressure, measurements of the intrajugular venous pressure were performed by the technic developed by Myerson, Halloran and Hirsch[3] and extensively used in the investigations of Myerson, Loman, Dameshek and Goldman.[4-7] The pressure within both internal jugular veins was equivalent to 300 mm. of water, and there was an excellent response to homolateral and contralateral jugular compression. Simultaneously, the venous pressure within one of the basilic veins was equivalent to only 80 mm. of water.

Following these studies, five venesections totaling 3060 cc. of blood were performed within 12 days, after which determination of the intrajugular and intraspinal fluid pressures was repeated. These were normal, the pressure within the internal jugular veins measuring 50 mm. and the general venous pressure measuring 30 mm. On October 16, there was complete regression of papilledema. On October 21, the disks were well outlined; there was no venous distention, and except for slight tortuosity of the blood vessels, the fundi were completely negative.

The patient remained moderately well with the use of occasional venesections. With lowering of the hemoglobin and hematocrit levels to near-normal values, there was a gradual diminution in dyspnea as well as an improvement in strength and well-being. A slight degree of optic atrophy of one disk persisted.

Death occurred suddenly in May, 1944, while the patient was seated. An autopsy was not performed.

Discussion

Although cases resembling the present one have been occasionally encountered, some of them having been operated on for cerebral neoplasm, the report of complete recovery from blindness as the result of bloodletting is almost unique. Through the bibliographic research of Dr. Camille Dreyfus, a case almost identical with ours was uncovered in one of the 1838 issues of the *Boston Medical and Surgical Journal*.[8] The case is reported as one of "amaurosis from plethora," and is reproduced in Figure 1.

The present case is an example of severe polycythemia secondary to long-standing bronchopulmonary disease. The chronic bronchial asthma and emphysema were probably productive of arterial anoxemia, which in turn resulted in stimulation of red-cell production and the gradual development of erythremia. Simultaneously, the pressure within the pulmonary circulation probably became increased, with gradual development of pulmonary-artery sclerosis and cor pulmonale. Cardiac manifestations in the presence of marked cyanosis and erythremia led Ayerza[9] to call these cases "*cardiacos negros*," and for a number of years the designation "Ayerza's disease" has often been used for these and similar cases.

The contrasts between this case of secondary polycythemia and one of the so-called "true" (vera) or idiopathic type are as follows:

	SECONDARY POLYCYTHEMIA	TRUE POLYCYTHEMIA
Pulmonary or cardiac changes	Present (chronic)	Absent (except as secondary phenomena)
Splenomegaly	Absent	Present
Cyanosis	Present (marked)	Absent
Arterial anoxemia	Present (marked)	Absent
White-cell count	Normal	Increased
Granulocyte count	Normal	Increased
Platelet count	Normal	Increased

In both secondary and primary types of cases there is an extreme increase in red-cell volume, with a resultant increase in blood viscosity, slowing of the blood flow and a tendency to the development of thrombosis.

CASE OF AMAUROSIS FROM PLETHORA,

TREATED SUCCESSFULLY BY LOCAL AND GENERAL BLOODLETTING, COUNTER-IRRITATION, LOW DIET, ETC.

[Communicated for the Boston Medical and Surgical Journal.]

SEPTEMBER 10th, 1836. Dr. J. H. Flint was consulted for a complete amaurosis of both eyes, by Mr. P., æt. 24. Vision had been impaired nearly a year The history and symptoms of the case were as follows.

He had for a number of months been the subject of momentary blindness, particularly under circumstances favoring a determination of blood to the brain, or interrupting the circulation through it. The failure of vision was sudden and total. The general health was much disordered, and he was subject to deep-seated, protracted headache. His habits were such as to promote a general fulness of the vascular system He had, for a long time, been the subject of repeated daily attacks of epistaxis, which were now partially suppressed, occurring not oftener than once or twice a week A month preceding the entire failure of vision, he sought medical advice for the severe headache which occurred in paroxysms from seven to twelve hours continuance. General bleeding, purging and blistering were persisted in for a number of weeks, without any perceptible benefit The epistaxis was almost entirely suppressed, and in a few weeks the failure of vision was constant and total.

When he applied for advice, all the symptoms concurred to indicate an active congestion of the cerebral vessels and compression of the optic nerve, as the probable cause of blindness.

With a view to diminish the general fulness of the vessels, particularly of the head, and equalize the circulation as far as possible, general and local bleeding were directed, in connection with vegetable diet, active counter-irritation, and such alterant and cathartic medicines as were necessary to secure a regular performance of the functions. The local bleedings were obtained by puncturing the nostrils, in imitation of the previous provision of nature by the former frequent epistaxis. Nothing could have been more happy in its immediate result than this simple practice of pricking the septum of the nostrils. There was a marked improvement after the continuance of it for three or four days, and each subsequent renewal of the hæmorrhage, which was promoted by sternutations, &c., illustrated the importance of this discharge

In the course of six weeks the power of vision was so far restored, that from being unable to distinguish the house wall from the window, he could mark and follow passing objects, especially on cloudy days and the hour of twilight. He noticed and picked up white objects, as bits of cloth and paper, from the floor It is to be regretted that he left the hospital at this time, when every day was rich in promise of a perfect cure, with the conceit that he and his friends were adequate to the subsequent management of the case.

After the patient left Dr Flint's care, the local bleedings were discontinued, and the blindness returned as completely as before In the course of six weeks he was seized with an apoplectic attack, from which he slowly recovered; thus proving, beyond a doubt, that the cause of amaurosis was to be found in the fulness of the cerebral vessels.

Northampton, February, 1838. J H WRIGHT, M.D

FIGURE 1.

Increased intracranial pressure has occasionally been noted in true polycythemia, and has at times led to the false diagnosis of intracranial neoplasm and even to surgical exploration. The mechanisms of the increased pressure have never been worked out. In the present case, although the increased pressure was obviously related to the effects of the rather than to actual thrombosis of the cerebral venous channels. With thrombosis of a lateral sinus, one would expect either low or absent pressure in the corresponding internal jugular vein. At the point at which the internal jugular pressure is measured the vein is contiguous to the outlet of the jugular bulb, where it receives no venous con-

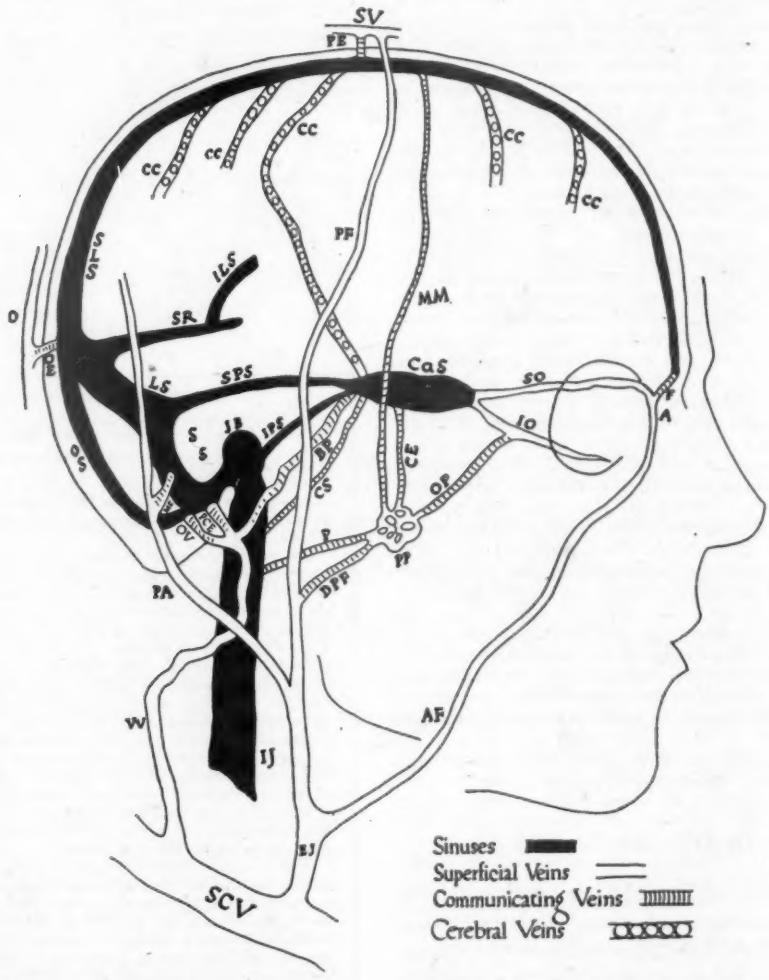

FIGURE 2. *Diagram Showing the Communications between the Dural Sinuses, the Cerebral Veins and the Superficial Veins (Modified from Braun[22]).*

A, *angular vein*; AF, *anterior facial vein*; BP, *basilar plexus*; CC, *superior cerebral veins*; CE, *communication between cavernous sinus and pterygoid plexus*; CaS, *cavernous sinus*; CS, *communication between cavernous sinus and internal jugular vein*; DPF, *deep posterior facial vein*; EJ, *external jugular vein*; F, *frontal vein*; IJ, *internal jugular vein*; ILS, *inferior longitudinal sinus*; IO, *inferior orbital vein*; IPS, *inferior petrosal sinus*; JB, *jugular bulb*; LS, *lateral sinus*; ME, *mastoid emissary*; MM, *middle meningeal vein*; O, *occipital vein*; OE, *occipital emissary*; OP, *communication between infraorbital vein and pterygoid plexus*; OS, *occipital sinus*; OV, *communication between occipital sinus and vertebral vein*; P, *pharyngeal vein*; PA, *posterior auricular vein*; PCE, *posterior condyloid emissary*; PE, *parietal emissary*; PF, *posterior facial vein*; PP, *pterygoid plexus*; SLS, *superior longitudinal sinus*; SCV, *subclavian vein*; SO, *supraorbital vein*; SPS, *superior petrosal sinus*; SR, *straight sinus*; SS, *sigmoid sinus*; SV, *scalp vein*; VV, *vertebral vein*.

disease, it was at first debatable whether this was due to cerebral venous thrombosis or to simple plethora of the intracranial venous system. The information gained by measurement of the pressure and the dynamic responses within the internal jugular circulation, together with the great diminution of the intrajugular pressure following several venesections, almost certainly pointed to the presence of plethora tributaries. Furthermore, if lateral sinus thrombosis were present, *jugular compression would effect no rise in the contralateral jugular pressure.* In this case the jugular pressure was not only equally high bilaterally but was increased by homolateral and contralateral jugular compression.

It is furthermore doubtful whether a simple thrombosis of the lateral sinus is sufficiently ob-

structive to the outflow of the intracranial blood to produce, except for a short time, an increased intracranial pressure, since a rerouting of venous circulation probably quickly occurs. This has been evident in those cases in which ligation of one or even both jugular veins has been performed in cases of thrombosis of the lateral sinus. Experimentally, Bedford[10] demonstrated that, although an increase in intracranial pressure follows ligation of both jugular veins or both lateral sinuses, the cerebrospinal-fluid pressure returns to normal within a few hours.

Furthermore, Hassin[11] has shown that thrombi that completely obstruct both the longitudinal and lateral sinuses have no effect on the absorption of the cerebrospinal fluid from the subarachnoid space. It is probable that under such conditions veins other than the longitudinal sinus are capable of absorbing the cerebrospinal fluid and keeping its pressure at normal values. In addition, if such vascular lesions were present, a return to a normal intracranial pressure should not be expected so soon after venesection. The likeliest explanation of the increased intracranial pressure in the case under discussion is therefore a great increase in cerebral venous pressure. This could be brought about by thickening of the blood, relative venous stasis or slowing and damming of venous blood in the rigidly enclosed sinuses and cerebral veins. The resulting increase in venous pressure would readily be reflected to the cerebrospinal fluid by way of the thin-walled cerebral veins.

The dissociation between the pressure in the internal jugular vein and that in the general venous system *in the absence of obstruction to cerebral venous channels* is a unique phenomenon. So far as we know, no other examples have been reported. Certain physical conditions unique to the intracranial cavity may predispose to such a dissociation in pressures. Thus the cerebral veins have features that differ in certain particulars from the veins elsewhere in the body. These may be listed as follows: complete rigidity of the cranial venous sinuses; lack of muscular fibers in the walls of the sinuses; great width of the lumens of the sinuses as compared with the small size of the veins that empty into them; entrance of the many cerebral veins into the longitudinal sinus *against* the current of blood flow; and tortuosity of the course of the sinuses. In the last, the longitudinal sinus splits at right angles at the torcula. The inferior part of the sigmoid sinus lies at a much lower level than the jugular bulb, which is much wider than the sigmoid sinus. As the sigmoid sinus enters the jugular bulb, there is a marked narrowing. There is also a marked narrowing at the exit of the jugular bulb (Fig. 2).

These characteristics seem designed to retard the flow of blood so that under certain conditions, such as sudden changes in posture, the brain is spared the sudden and full brunt of extreme vascular changes in pressure. When, however, the venous circulation is already overtaxed, as in polycythemia, it is possible that further slowing, in some cases to the point of thrombosis, may be enhanced by these peculiarities of the intracranial venous system and result in a great increase in cerebral venous pressure.

Another possibility that must be considered in any dissociation of the cerebral and the general venous pressure is the presence of an obstructing lesion of the neck or mediastinum, with compression of the great veins. There was no evidence of such an abnormality in the present case. It is furthermore obvious that a rise in cerebral venous pressure by this type of obstruction could not be relieved by venesection alone.

Summary and Conclusions

A case is reported of severe secondary polycythemia with increased intracranial pressure, choked disks and amblyopia, in which dissociation between an increased internal jugular venous pressure and a normal general venous pressure was present. Following venesection therapy, the cerebrospinal-fluid pressure and intrajugular venous pressure became normal, and there was complete regression in all the symptoms referable to the head.

The possible mechanisms for the dissociation between intrajugular and general venous pressures, with the resulting great increase in cerebrospinal-fluid pressure, are discussed.

Other possible causes of this dissociation, including thrombosis of the lateral sinus, are discussed, and excluded as having no bearing in the present case.

A study of the intrajugular dynamics may be diagnostic in the determination of the presence or absence of thrombosis of the lateral sinus.

Severe headaches in polycythemia may be caused by an increased intracranial venous pressure, with a resultant increase in cerebrospinal-fluid pressure.

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PSYCHOSOMATIC INTERRELATIONS IN GENERAL MEDICINE

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THE efficiency of the general medical practitioner is conditioned by the following factors: first, his knowledge and appreciation of the normal human organism as a complex and integrated whole of physical, mental and emotional elements and his understanding and appreciation of the types of pathologic variations from normality that may arise, with their respective symptomatology and etiology; second, his knowledge of how to determine the nature and extent of these variations; and third, his selection of treatment.

Knowledge and appreciation of the normal human organism of integrated physical, mental and emotional elements include the following concepts: the body as a mechanism made up of cells performing proper physiologic functioning; the nervous system, of which the brain is the integrating center and through which activity of the biologic organism functions from within in a relation compatible to its environment; consciousness, the main function of the brain through which the mind is made rationally aware of the motivating biologic forces in the organism; the emotions, serving as well-balanced, subjective feeling-reactions to perception of these forces; personality, or the subject's usual manner of handling these forces in accordance with his best social adjustment; thoughts and ideas, which are concepts arising from these forces as highly developed adaptations of them to the environment; conscience and ideals, or the ethical and esthetic resultants arising from the mental and emotional conditioning of these forces; and the normal life of the normal human organism, which essentially consists in satisfying these forces — needs, urges and responses — in accordance with conscience and ideals.

An attempt has been made through this brief analysis of the normal human organism, with its balanced, co-ordinated psychosociobiologic functioning, to establish the concept of it as a complex and integrated whole.

Consideration of the pathologic variations that may occur in the normal human organism, with their respective symptomatology and etiology, includes the concepts of pathologic disturbances ranging from trauma of cellular tissue to tensions in the highest levels of the brain. If emotional tensions affect the lower levels of the nervous system and are mediated through the autonomic system, they cause a disturbance called "organ neurosis." In this condition the somatic component is the most pronounced element. If emotional tendencies develop and affect the highest levels of the brain, they cause neurotic and psychotic disturbances, which are evidenced in thought and behavior. In these cases the psychic symptoms are most evident. Any disruption of balanced, co-ordinated psychosociobiologic functioning in the human organism results in its disintegration or in a pathologic condition.

Clinical study has revealed that in the investigation of functional disturbances there are specific correlations between emotional constellations and physiologic responses. The psychosomatic conditions resulting from these functional disturbances are called "psychosomatic symptoms."

Psychosomatic symptoms are present in all disease. Their psychic and physical components are in direct ratio to the degrees of psychologic and physical etiologic forces involved. Menninger† has classified disease in five groups, and indicates the relative degrees of symptomatic expression in terms of psychic reaction and physical reaction for each group. In Group 1, with a valence of 5 on the psychic reaction and a valence of 1 on the physical reaction, are included all the severe functional mental diseases referred to as psychosis. In Group 2, with a valence of 4 on the psychic reaction and a valence of 2 on the physical reaction, is included a class of illnesses generally regarded as mental in that the causative factors are chiefly psychologic but are always associated with physical symptoms, which are often treated as if they were the sole causes. In Group 3, with a valence of 3 on the psychic reaction and a valence of 3 on the physical reactions is included a heterogeneous assortment of diseases — first, organic brain diseases; second, the endogenous toxic and infectious illnesses in which the mental symptoms are produced by toxins; and third, a host of physical diseases that masquerade under the guise of mental symptoms, often appearing to be primarily mental. In Group 4, with a valence of 2 on the psychic reaction and a valence of 4 on the physical reaction, is placed a large class of organic illnesses frequently found in persons in whom are discovered conspicuous psychologic maladjustments but whose complaints are physical and whose diseases are manifested in organic disease. In Group 5, with a valence of 1 on the psychic reaction and a valence of 5 on the physical reaction, are found a great number of illnesses in which almost the entire emphasis seems to be on the somatic side but in which the psychic component, even though inconspicuous, is of great importance.

If the concepts of the human organism as an integrated whole and of disease as the psychosomatic expression of this biologic unit are accepted, the general medical practitioner must seek the etiology

*Physician to the Horn Home for Aged Couples, Lowell.

†Menninger, W. C. Psychological factors in disease. *Wisconsin M. J.* 37:29-38, 1938.

of disease in the constitution and in exogenic, psychologic and social factors. Until recent times the training that most physicians received failed to include any practical, systematic knowledge of such therapeutics. Consequently, many of those who can find no organic disease in a patient attempt to convince him that he is suffering only from "tired nerves" or "imagination." The dissatisfied patient who has received such a diagnosis seeks the services of physician after physician. Each in turn gives him a similar interpretation, none considering factors other than somatic symptoms to be pertinent to his condition.

The following three illustrations, similar to cases in the everyday experience of the general medical practitioner, bear out the truth of the above statements. In each of them the patient had consulted several physicians and had been given only drug therapy.

Case 1. H. Se, a 45-year-old man, with a wife and five children, had been unemployed and unable to secure employment for a period of 11 months. He complained of gastric pain 1½ hours after eating; this condition was relieved only by taking more food or by alkaline therapy. His symptoms were a very poor appetite, insomnia and marked loss of weight, due to restricted diets given by various clinics and physicians. X-ray examination showed an ulcer situated near the pyloric end of the stomach. The patient was given various kinds of alkaline drugs, to no avail. During consultations the fact became evident that extreme worry over his financial situation was responsible for many of his symptoms. Employment was secured for him. In less than a month his condition was normal in every respect, and it has remained so for over 15 years.

Case 2. An 80-year-old man was confined to bed suffering with a peritonsillar abscess. He was unable to take nourishment because of the throat condition. The treatment given failed to effect a spontaneous cure, so that he became convinced that the attending physician could do nothing for him. He insisted that he had carcinoma of the throat and that no one would tell him the truth. He refused food and medication, wishing only to hasten his end so that he might be spared pain. He lost 30 pounds in 2 weeks. He finally consented to consult a nose-and-throat specialist, who after examining him remarked that what he could see was "all right" but that there was possibly "something lower down in the larynx." The physician suggested an x-ray examination, which was made. The patient insisted on telling the roentgenologist exactly where to look and what to do. After being assured that there was no disease in his throat and that an elongated uvula caused the tickling and cough, the patient returned to his home, where he was given a sedative for one night's sleep and placed on a high-calorie and high-vitamin diet. His recovery was rapid and complete.

Case 3. An extremely nervous and emaciated 15-year-old girl, who was a bed patient, complained of nausea, vomiting, pain over the lower abdominal region, constipation and scanty and irregular menstrual periods. Repeated enemas brought no relief. The patient lived with her family, the members of which were neurotic. Physicians had referred her to a surgical service, where she had been told that she must undergo an operation if she wished to live. She became hysterical. Since no diagnosis calling for surgery had been given, the attending physician decided on medical treatment. After elevation of the foot of the bed to help the abdominal organs to rise out of the pelvis, regulation of the diet and the giving of clyses to restore the lost body fluid and of sea moss and mineral oil for the constipation, vomiting stopped in 1 week and the patient became free from pain and much more cheerful. A ptosis belt was used to hold up the organs until she gained weight. The physician established a situation in the home that resulted in the proper adjustment of the patient. She was soon able to carry on like other normal girls of her age, and has experienced no return of pain or of fear for the last 6 years.

In all these cases the abnormal condition was chiefly due to a personality disorder, but the psychic component of these conditions had been disregarded. Since 50 per cent of the cases coming to general medical practitioners may be placed in this group of so-called "biologic functional disorders," the urgent need for the revision and expansion of modern medicine in postgraduate and undergraduate medical education is evident.

Medical colleges must provide for the training and education of all physicians in the field of personality disorders, including their recognition, their symptomatology, their scientific treatment and their prevention. Such training and education demand the inclusion of psychiatry as a basic medical subject and the compulsion of everyone practicing medicine to become as firmly grounded in this field as he is in other basic medical subjects.

Orientation courses in psychiatry, dealing with the emotional factors in the general medical and surgical patients in whom the symptoms of functional illness are most frequently encountered, should be given for the benefit of those medical practitioners who have little knowledge of or training in psychiatry and psychiatric technic. Only when anatomy, physiology and the chemistry of the body are studied in relation to biologic functioning can a true diagnosis of its pathologic variations from normality be made and proper therapeutic treatment be applied.

Summary

The normal human organism is a psychosociobiologic whole, and any disruption of the co-ordinated functioning of this whole results in a pathologic condition, which is evidenced by psychosomatic symptoms. The general medical practitioner should be able to recognize these psychosomatic symptoms, to make the correct diagnosis and to apply proper treatment. Current practice in medicine should include the use of psychiatry, since only in this way can the psychic and the somatic components in a patient be studied in their proper relation.

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MEDICAL PROGRESS

THE TREATMENT OF INFECTIONS WITH PENICILLIN*

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PENICILLIN is now well established as an effective chemotherapeutic agent for the treatment of many infections. During the past year so many reports attesting to this fact have appeared in the American and English literature that to review them all in a single paper is not possible. The purpose of the present article is to summarize such principles of penicillin therapy as have evolved from the investigations of the past five years and to present the current views on the use of penicillin in the more important infections that are encountered in civilian practice. It is recognized that experience with penicillin is enlarging so rapidly that some or many of these views may be outdated before this article reaches print.

The history of the discovery of penicillin by Fleming[1] in 1928 and of its later development as a practical chemotherapeutic agent by Florey and his associates[2] is now well known by the medical profession and will not be reviewed. Likewise, it is beyond the scope of this paper to recount the fascinating story of how the large-scale production of the drug was achieved in the face of many difficulties.[3, 4]

CHEMISTRY

The published information regarding the chemistry of penicillin is meager. Abraham and Chain[5] have reported that penicillin is an organic acid. Since the free acid is quite unstable, however, only the more stable sodium and calcium salts of penicillin are prepared for clinical administration. These two salts do not differ in therapeutic activity or toxicity. The calcium salt has the advantage that it is less hygroscopic and therefore can be used in powdered form with greater ease.

It is now known that the mould *Penicillium notatum* actually produces several types of penicillin. Sir Henry Dale[6] has recently revealed that three penicillins have already been isolated in the pure state. These are known in the United States as penicillins F, G and X, and in England as penicillins 1, 2 and 3, respectively. Dale states: "All these penicillins have the specific remedial action in high, though not quite identical degrees, and there are proportional differences, still to be explored, in their proportional efficiencies against different infective organisms. Penicillin G or 2 is the penicillin which is predominant in most preparations now available." Penicillin G was the first to be obtained in pure crystalline form, the isolation of the crystalline sodium salt being accomplished by MacPhillamy and Wintersteiner of the Squibb Institute in July, 1943.[3] This material was found to contain about 1650 Oxford units per milligram.‡

Recently the International Conference on Penicillin[7] has recommended that an international penicillin standard be prepared from crystalline sodium penicillin G and that the international unit of penicillin be defined as the specific penicillin activity contained in 0.6 micrograms of the international penicillin standard. The international unit so defined is approximately equivalent to the Oxford unit.

Although pure crystals of penicillin were first isolated almost two years ago, synthesis of the drug has not yet been accomplished. All the drug produced today is recovered from culture liquor in which *P. notatum* has grown. Because a large amount of active drug is lost in preparing crystalline penicillin, this material is not available at present for the routine treatment of patients. The preparations that are used in clinical practice assay roughly between 200 and 1000 Oxford units per milligram. It is thus evident that they contain between 37 and 88 per cent of impurities.

The preparations of penicillin that were first employed clinically were found to be relatively unstable both in powder form and in solution. The more recently prepared commercial products are a great deal more stable. Kirby[8] has shown that solutions of penicillin may be kept at room temperature (22° C.) for one week without evidence of deterioration and that most lots of penicillin retain their full activity in solution for ten to twelve days. At 37° C., however, full potency persists for only four days. As a dried powder the drug is even more stable. Regna's[9] studies indicate that there is no loss of potency during a period of at least three hundred and fifty days when the powder is stored at 0-5°C. Even at 37° C. the powder will retain full potency for at least sixty days.

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‡Chemical assay of penicillin is not yet possible. The drug is assayed therefore in terms of its antibacterial activity. The Oxford unit is defined as "that amount of penicillin which, when dissolved in 50 cc. of meat-extract broth, just completely inhibits the growth of the test strain of *Staphylococcus aureus*."

Preparation of Solutions

For clinical administration penicillin is usually dissolved in physiologic salt solution, although distilled water and 5 per cent dextrose solutions are also satisfactory solvents. Penicillin is extremely soluble and the concentrations employed can be varied with the method of administration, for example, from 250 units per cubic centimeter for local application to superficial wounds to 100,000 units per cubic centimeter when large doses are being given intramuscularly. For intramuscular use a concentration of 5000 units per cubic centimeter permits the giving of doses up to 15,000 units without undue discomfort, and the amount of drug lost by the adherence of the solution to the bottle and syringe and in other unavoidable ways is less than when higher concentrations are used. Since penicillin solutions are not self-sterilizing, care should be taken to avoid contamination while the solutions are being prepared and administered.

Pharmacology and Methods of Administration

Early studies of the pharmacologic properties of penicillin by Florey and his associates[10] and by Rammelkamp and Keefer[11] indicated that certain inconveniences would have to be contended with in the clinical administration of penicillin. Oral administration was found to be ineffective because the drug so given was largely inactivated by the hydrochloric acid of the gastric juice. Many ingenious attempts have since been made to overcome this difficulty, but no effective method of administering the drug orally in moderate dosages has yet been discovered.[12] The rectal instillation of penicillin was also found to be ineffective because the drug was rapidly inactivated by the intestinal bacteria.

Fortunately it was found that penicillin could be administered intravenously or intramuscularly without untoward reactions and that effective blood levels could be achieved when the drug was so administered. The same studies revealed, however, that, owing to the rapid excretion of penicillin in the urine, blood levels were not well maintained. In patients with normal renal function about 60 per cent of the amount injected was excreted in the first hour. This rate of excretion was found to vary little, if at all, with the size of dose administered, although with large doses detectable concentrations of penicillin in the blood persisted longer than with small doses. Thus, when large doses, such as 50,000 and 100,000 units, were given in a single injection, small amounts of drug were found in the blood for as long as four to six hours. Fleming et al.[13] have pointed out, however, that a continuous bacteriostatic level can be obtained in the blood much more economically by the use of small doses, such as 15,000 units, given every two or three hours than by the administration of large doses at only slightly longer intervals, and this has been confirmed by clinical experience.

After the intramuscular injection of a given dose, an effective blood level was found to be maintained for a slightly longer period of time than after the intravenous injection of a similar quantity of drug. This observation, together with the greater ease of administering the drug intramuscularly, led most workers both in England and in the United States to follow the Floreys[14] in using the intramuscular route for the routine treatment of patients. It is now well established on the basis of clinical experience that this route is fully as effective therapeutically as the intravenous route.

Early attempts to administer the drug subcutaneously revealed that absorption from the subcutaneous tissues was slow and irregular,[11] and in addition it was found that subcutaneous injection was often quite painful. More recently it has been reported that absorption after subcutaneous administration does not differ significantly from absorption after intramuscular injection.[13, 15] It is likewise stated that with the present preparations of penicillin, subcutaneous injection is not significantly more painful than is intramuscular injection. Herwick et al.[16] have shown that there is a significant correlation between the purity of a penicillin preparation and the irritation resulting from its intramuscular injection. It is therefore not unlikely that, as purer and less irritating commercial penicillin becomes available, the subcutaneous administration of the drug may be more widely practiced.

Several attempts have been made to obviate the need for frequent injections and the irregular blood concentrations that result from this method. Administering penicillin by a continuous intravenous infusion has been the method most frequently used. Some investigators[17] believe that this is the method of choice and use it routinely. Other workers[15, 18] think that the inconveniences encountered in maintaining a constant intravenous infusion, together with the fairly frequent development of painful thrombophlebitis, outweigh its possible advantages.

More recently the use of a continuous intramuscular infusion has been recommended.[19] The total twenty-four-hour dose of penicillin can be administered in a volume of 200 cc. to 500 cc. without undue discomfort into the lateral muscle of the thigh, and quite uniform blood levels can be maintained.[20] The levels achieved by this method are approximately the same as those obtained by the continuous intravenous infusion of the same dosage of penicillin.

Two other methods designed to reduce the number of injections have recently been reported. Romansky and Rittman[21] have stated that mixtures of penicillin in beeswax and peanut oil, when injected intramuscularly, are slowly absorbed and that therapeutic levels of penicillin can be detected

in the blood for six to seven hours after a single injection. The practicability of this method for prolonged therapy is being investigated.

Rammelkamp and Bradley[22] demonstrated in 1942 that when Diodrast is administered simultaneously with penicillin it partially blocks the excretion of penicillin by the renal tubules. More recent experiments with the use of *p*-aminohippuric acid in animals and in man have shown that this substance also partially blocks the excretion of penicillin and prolongs the time during which it can be detected in the blood stream.[23, 24] This method requires further study before its general adoption can be recommended.

Theoretically the maintenance of a constant blood level of penicillin would appear to be desirable therapeutically, and it might be expected that methods of administration that would provide such a blood level would be the most effective clinically. Actually, there is as yet no convincing evidence that a given daily dose of penicillin is more effective when given by a continuous infusion than when it is administered by intermittent intramuscular injection at three-hour intervals. Further study of this problem is needed.

The distribution of penicillin in the body after intramuscular or intravenous injection has been studied by many workers. The results of these studies contain valuable therapeutic implications.

In patients without meningitis, penicillin cannot be detected in the cerebrospinal fluid after the intramuscular or intravenous injection of the usual therapeutic doses. When large doses of penicillin are administered to such patients, however, minute amounts of the drug are occasionally demonstrable in the spinal fluid.[25] Recently there have been reports of the passage of penicillin from the blood into the spinal fluid of patients with purulent meningitis.[15, 26, 27] The concentration of drug found in the spinal fluid was markedly less than that present in the blood, and in several cases it did not constitute an effective therapeutic level.

There is good clinical evidence that the amount of penicillin that reaches the spinal fluid in bacterial meningitis is probably insufficient to control the infection. Several cases are known in which no improvement either in the clinical condition of the patient or in the spinal-fluid findings resulted after several days of systemic penicillin therapy, but in which prompt improvement followed the intrathecal administration of the drug. Also several cases are known in which meningitis appeared during the course of the intramuscular or intravenous treatment of an extrameningeal infection. In these cases, likewise, no improvement took place until intrathecal therapy was instituted.

Penicillin diffuses poorly, as a rule, into the pleural cavity, and although prolonged intramuscular therapy may occasionally control an infection of the pleura, the introduction of penicillin into the empyema cavity is recommended as a more economical and certain form of therapy.[28]

Penicillin has been detected in ascitic fluid and in synovial fluid in significant concentration after parenteral administration.[15, 25, 29] Occasional cases of suppurative arthritis have responded to systemic treatment. Local treatment, whenever possible, seems to be desirable, however, since penicillin does not injure the joint and systemic therapy may be unsuccessful.[30]

Struble and Bellows,[31] working with dogs, have shown that penicillin administered systemically in amounts comparable to therapeutic doses reaches such a slight concentration in the fluids and tissues of the eye that it is not measurable by the usual methods of assay. Von Sallmann[32] has stressed the need for employing iontophoresis or a corneal bath to secure an adequate penetration of penicillin into the aqueous humor. Penicillin is excreted in the bile in higher concentrations than it is found in the blood.[33] The drug has not been detected in saliva, tears, pancreatic juice, succus entericus or gastric juice.

Antibacterial Action

Penicillin is highly selective in its antibacterial activity. In-vitro tests and a study of experimental infections in animals have indicated clearly in what infections penicillin therapy may be of value and in what infections it cannot be expected to have any effect. Table 1 lists the important pathogenic organisms against which penicillin has been found to be active by laboratory studies. In general, penicillin has proved to be effective against infections caused by these organisms, although in single cases the site or extent of the infection, the general condition of the patient or the presence of complications may preclude successful therapy.

Table 1. *Organisms Susceptible to the Action of Penicillin.*

Staphylococcus aureus	*Clostridium novyi*
Staphylococcus albus	*Clostridium oedematis-maligni*
Streptococcus pyogenes	*Clostridium perfringens*
Nonhemolytic streptococci	*Clostridium tetani*
Anaerobic streptococci	*Corynebacterium diphtheriae*
Diplococcus pneumoniae	*Treponema pallidum*
Neisseria gonorrheae	*Treponema pertenue*
Neisseria intracellularis	*Streptobacillus moniliformis*
Bacillus anthracis	*Spirillum minus*
Clostridium botulinum	*Borrelia novyi*
Clostridium histolyticus	*Actinomyces bovis*

Among bacterial species usually susceptible to penicillin, occasional strains are encountered that are naturally resistant to the drug. The susceptible species in which naturally resistant strains have been reported are staphylococci, nonhemolytic streptococci and anaerobic streptococci.[34, 35]

Reports on the effectiveness of penicillin therapy in experimental Weil's disease differ. Heilman and Herrell[36] reported no deaths from the disease in

32 guinea pigs treated with penicillin and a mortality rate of 91 per cent in an equal number of untreated controls. Augustine et al.,[37] also using guinea pigs, found penicillin had no curative value after the appearance of clinical manifestations of the disease.

The action of penicillin on viruses and rickettsia is likewise not wholly clear. Heilman and Herrell[38] have reported that mice infected with the viruses of ornithosis and psittacosis can be protected by penicillin, whereas Moragues, Pinkerton and Greiff[39] have shown that penicillin therapy reduces the mortality in mice infected with murine typhus fever. In both studies the dosage per kilogram of body weight was far in excess of that necessary in clinical practice to control infections caused by susceptible bacteria. To date no convincing reports have been published to indicate that penicillin is effective in any virus or rickettsial disease in man. When such infections are complicated by secondary infections due to organisms that are sensitive to the drug, the latter may be successfully treated with penicillin.[40]

In contrast to the susceptible species, many important pathogenic bacteria are not adversely affected by the concentrations of penicillin that can be achieved in the blood and tissues (Table 2).

TABLE 2. *Organisms Not Susceptible to the Action of Penicillin.*

Escherichia coli	*Haemophilus ducreyi*
Eberthella typhosa	*Streptococcus faecalis*
Shigella dysenteriae	*Brucella melitensis*
Salmonella paratyphi	*Vibrio cholerae*
Salmonella enteritidis	*Pasteurella pestis*
Proteus vulgaris	*Pasteurella tularensis*
Pseudomonas aeruginosa	*Mycobacterium tuberculosis*
Klebsiella pneumoniae	*Plasmodium vivax*
Haemophilus influenzae	Yeasts
Haemophilus pertussis	Molds

These species are generally considered to be insensitive to penicillin. Actually several of these species can be inhibited in vitro by the use of relatively high concentrations of penicillin, indicating that penicillin insensitivity is often a relative rather than an absolute quality.[41] For practical purposes, however, it is recognized that penicillin has no effective clinical action against these organisms.

The development of resistance to penicillin by bacteria as the result of exposure to sublethal concentrations of the drug either in vitro or in vivo has been reported by several workers.[42, 43] There is some laboratory evidence to indicate that organisms that develop resistance to penicillin in vitro may become less virulent.[44, 45] Observations of this kind have not yet been made in human infections.

The antibacterial action of penicillin in vitro may be either bactericidal or bacteriostatic.[46] Most authorities are agreed that in the treatment of human infections its action is bacteriostatic. Penicillin inhibits the growth and multiplication of bacteria, but the actual destruction and elimination of the infecting organisms are probably effected by the normal defense mechanisms of the host. This conclusion is well substantiated by clinical experience. With the exception of uncomplicated gonorrhea and meningococcemia, treatment with penicillin has not proved to be effective in any disease unless it has been continued for at least twenty-four to forty-eight hours, and in the great majority of cases much longer periods are necessary.

Florey et al.[10] early reported that serum, pus, peptones and the breakdown products of tissue autolysis do not inhibit the action of penicillin, a distinct advantage for this drug over the sulfonamides in many types of infection. Bigger[47] has recently reported that human serum does inhibit the action of penicillin. He attributes this phenomenon to the absorption of penicillin inactivators formed in the intestinal tract.

It is now well known that *Escherichia coli* and certain other bacteria insensitive to penicillin produce a substance that inactivates penicillin. This substance has been named "penicillinase."[48] Penicillinase can be prepared by various means,[49–51] and its incorporation in culture mediums to inactivate penicillin present in the blood and exudates of patients receiving the drug has been suggested. Experience, however, does not indicate that penicillinase has the same practical value that *p*-aminobenzoic acid has in inhibiting sulfonamide activity in culture mediums. Thus, when duplicate cultures with and without penicillinase are made, the number of additional positive cultures obtained is insignificant.[20]

Several different methods have been described for determining the concentrations of penicillin in the blood and body fluids.[52–54] All these methods involve the titration of the antibacterial activity of the unknown specimen against an organism of known sensitivity to penicillin. Although such methods are admittedly crude, they permit an estimation of penicillin concentration that is satisfactory for clinical purposes. The equipment and technical skill necessary to perform these tests are not beyond the reach of the average bacteriologic laboratory, but the information that is gained does not seem to be sufficiently helpful to warrant the routine determination of penicillin blood levels in clinical practice. The clinical response to treatment is, in most cases, all that is needed to determine dosage.

A somewhat more useful test for clinical purposes is the determination of the sensitivity of various organisms to penicillin.[42] In the great majority of cases one can rely on the bacterial species alone as an indication of susceptibility. In particular cases, however, especially those that do not respond to penicillin in the expected manner, determination of the susceptibility of the patient's organism to penicillin is of value.

Clinical Administration

A number of papers dealing with the general aspects of penicillin therapy have been published by several different groups of investigators.[10, 14, 17–18, 29, 55–60] These reports describe the experiences of the various authors with a wide variety of infections. Although there have been differences in the details of treatment, the observations of the various groups are in general agreement. These papers will not be reviewed separately since it would appear more profitable, in discussing the clinical use of penicillin, to follow so far as it is possible an outline based on etiology. The views expressed in these articles will be reflected in the subsequent sections that deal with the treatment of specific infections. To avoid repetition, problems having to do with the site of the infection rather than the etiology of the process will be discussed first. At the end of the paper, recent work on the adaptation of penicillin to problems encountered in certain medical specialties will be considered.

Local Factors

In the section of the pharmacologic properties of penicillin, it has already been mentioned that it appears necessary in the treatment of bacterial meningitis to administer the drug intrathecally. The lumbar sac has been used by most investigators for this purpose, since the drug apparently diffuses from this site throughout the entire subarachnoid space in most cases. There appears to be no need, therefore, to introduce the drug into the cisterna magna or into the ventricles through burr holes, except in unusual circumstances. Twenty-four hours after a single intrathecal injection of penicillin a therapeutic level of the drug can usually be detected in the cerebrospinal fluid. Hence, one intrathecal injection a day is probably sufficient, although many workers prefer to give the drug every twelve hours for the first two to four days of treatment. Solutions containing 5000 to 10,000 units per cubic centimeter are usually employed, and with doses of 10,000 to 20,000 units no significant untoward effects have been observed. Until experience has shown that larger doses can be given with equal safety, it does not seem advisable to give more than 20,000 units in a single injection since this dose usually produces an adequate level of penicillin for at least twelve to twenty-four hours. Because the diffusion of penicillin through the subarachnoid space occasionally may be imperfect for one reason or another, it is strongly advisable, whenever the infecting organism is susceptible to the sulfonamides, to give full doses of an effective sulfonamide concomitantly with penicillin.

In the treatment of empyema the local instillation of penicillin is also recommended.[28] The irrigation of the cavity with physiologic saline solution after the aspiration of whatever pus or fluid is present and before the introduction of penicillin is helpful. Intrapleural injections need be given only once every twenty-four to forty-eight hours, but a minimum of three injections is usually necessary to effect cure, and occasionally more prolonged treatment is required. Solutions containing 1000 units per cubic centimeter are usually employed, although the size of the cavity may make higher or lower concentrations desirable to ensure that the drug is brought into contact with all parts of the cavity.

In suppurative arthritis the local instillation of penicillin, whenever possible, is recommended. Although certain patients have responded to the systemic administration of the drug, this form of treatment is unreliable.

The treatment of bacterial endocarditis, regardless of the etiologic agent, requires prolonged therapy. Not infrequently the blood culture becomes negative after one or two days of treatment and the patient may show striking clinical improvement. Unless treatment is continued for at least two weeks, however, the chances of obtaining a lasting arrest of the infection are small.

The local use of penicillin without concomitant systemic administration in the treatment of soft-tissue wounds and superficial infections of the skin and subcutaneous tissues is occasionally effective.[14] When there is any significant area of cellulitis, however, the systemic administration of penicillin is usually necessary to obtain a maximum therapeutic effect. In selected cases, local penicillin therapy may often be combined with systemic therapy to good advantage. Penicillin is of no value when used as an irrigating solution, since it must remain in contact with infecting organisms for at least six to eight hours before it exerts its maximal antibacterial action.

Dosage

The problem of what constitutes an optimal dosage for the various infections treated with penicillin still requires extended investigation. It seems fairly clear that with the use of very large doses the results obtained are not superior to those following the use of moderate doses. Although excessive dosage has not been shown to be harmful to the patient, it constitutes a waste of a drug that is still not available in amounts sufficient to meet all the demands for its use. Once an effective bacteriostatic level of penicillin is achieved in the tissues, little seems to be gained by increasing the concentration in the tissues. Time is required for the natural defense mechanisms of the body to destroy the infecting organisms. It is doubtful whether this time can be shortened by increasing the dosage of penicillin excessively.

In most infections in adults, a dosage of 15,000 units given intramuscularly every three hours is usually effective. Exceptions to this rule will be

mentioned in the sections that follow. For children it appears that, depending on the size of the patient, from one half to one quarter of the adult dosage is usually adequate.[15, 61]

It has been implied in discussing the action of penicillin that, since the drug is bacteriostatic rather than bactericidal, treatment must be continued until the infection is eradicated or the signs of active infection may reappear. No hard and fast rules have been formulated concerning how long treatment should be continued. In general, penicillin has been given until the temperature has been normal for at least forty-eight hours or until the signs of active infection have been absent for a similar period. In many infections, such as meningitis, bacterial endocarditis, and osteomyelitis, it has usually been necessary to continue treatment for one or more weeks after apparent clinical recovery.

(To be concluded)

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 31141

PRESENTATION OF CASE

A sixty-year-old laborer was admitted to the hospital because of dysphagia.

Sixteen months before admission the patient was unable to swallow solid foods for a period of one week. The food stuck in the lower esophagus and refused to pass into the stomach. This symptom disappeared and he had no more trouble until seven months before entry, when one morning he was unable to swallow his breakfast of oatmeal and prunes. The food was apparently arrested in the lower esophagus and had to be regurgitated, although on the previous day no difficulty whatever had been experienced. Since that time he had repeatedly tried to swallow solid and semisolid foods without success and had subsisted on a liquid diet. After the onset of this difficulty, the passage of food caused burning pain at the lower end of the esophagus. He had lost 12 pounds and had become weak and tired easily. He had never vomited blood or passed bloody or tarry stools. For the previous four years he had worked in a mill scouring wool. He had had a mild nonproductive cough in the evening for the past three or four months. For a year and a half he had had rather sharp nonradiating, precordial pain that came on during exertion and lasted a few minutes; this occurred one to several times a week. For six months he had had dyspnea on exertion and ankle edema.

Physical examination revealed a well-developed, fairly well-nourished, pale man. The skin was dry, and there was little subcutaneous fat. Many teeth were carious, with broken retained roots. The pharynx was moderately injected. Examination of the lungs was negative, no rales being heard. The heart was slightly enlarged to the left. A Grade 2 systolic murmur was heard over the apex and was transmitted over the entire precordium. The abdomen was negative. The ankles showed slight edema.

The temperature, pulse and respirations were normal. The blood pressure was 156 systolic, 62 diastolic.

Examination of the blood showed a red-cell count of 3,470,000 and a white-cell count of 5750, with 60 per cent neutrophils. The blood prothrombin time and the serum nonprotein nitrogen, chloride and protein levels were normal. The urine was negative.

X-ray examination of the teeth revealed retained, decayed root fragments surrounded by abscesses in the upper and lower jaws. X-ray films of the chest showed clear lungs, with no evidence of metastases or other abnormality. The heart was prominent in the region of the left ventricle, and the aorta was tortuous. The ribs showed no destruction. A barium swallow revealed normal function; the esophagus was dilated to a point 9 cm. above the diaphragm, at which level there was sudden and constant narrowing, with failure to distend and with absent peristalsis. An ulcer crater 6 mm. in diameter was present about 1 cm. below the top of the narrowing. Immediately below the narrowing, which extended for about 1 cm., there was dilatation to a maximum of 5.2 cm., which contracted readily and revealed what resembled gastric mucosa in a hiatus hernia (Fig. 1). The remainder of the stomach and duodenum was negative. The patient's teeth were extracted and he was given several transfusions.

FIGURE 1. *Roentgenogram Showing Obstruction in the Esophagus and the Herniated Portion of the Stomach Below It.*

One week after admission an esophagoscopy was performed.

*On leave of absence.

Differential Diagnosis

Dr. Richard H. Wallace: May we see the x-ray films?

Dr. George W. Holmes: The first film of the chest shows the emphysematous chest of an old man, without anything definitely wrong. There is, perhaps, slight prominence of the left side of the heart and of the pulmonary vessels, but all these things can be discounted so far as the diagnosis is concerned. The important thing is the stricture in the esophagus, with only a moderate amount of dilatation. In the description one gets the impression that there was dilatation well above the diaphragm, and unless the stomach was herniated and the cardia was at that level instead of where it should have been, it would be unusual for the portion of the esophagus below the stricture to be dilated.

Dr. Wallace: Is it likely that part of the stomach had herniated through?

Dr. Holmes: That is a good possibility. In this small film I presume that this is a part of the stomach.

Dr. Wallace: Where is the ulceration?

Dr. Holmes: In this area here. I think that I can say that this was not cardiospasm and that the patient had an ulcerating lesion in the esophagus. The whole question is whether it was benign or malignant.

Dr. Wallace: There is mention of a break in the mucosa, as well as rigidity, without passage of peristalsis. Does that represent the whole area?

Dr. Holmes: I think so, but I must say that observations of that sort are not too reliable. They are difficult to make, and I should not want the diagnosis to hinge on that observation. The fact that the esophagus was not much dilated is against a long-standing lesion. If it was a benign ulcer it must have been fairly acute.

Dr. Wallace: This man had heart disease, which is incidental to our problem. At the time of onset one might have thought of the possibility of foreign body, but there is nothing in the history to bear that out. I should like to recall that most persons who get into trouble with a chicken bone or other foreign bodies have an artificial upper plate. Apparently this man did not have one; although there is no mention of it, it is stated that he had upper and lower teeth, which were later extracted. Also, there is nothing in the history about the swallowing of acid or alkali or anything else that might have given him a lesion in the esophagus. He had some anemia, and I merely mention the fact that he might be included in the group of patients with anemia from iron deficiency and avitaminosis, associated with dysphagia — the Plummer–Vinson syndrome. That syndrome, however, is classic in women and, furthermore, there is no mention of any difficulty in the mouth or the upper respiratory tract.

I am interested in the fact that this man was a woolsorter and I wondered if he could have had anthrax of the esophagus. I doubt that he could. Tuberculosis of the esophagus is really quite rare. It does occur, most generally in the presence of widespread tuberculosis, which this man apparently did not have. It is possible to have tuberculous involvement of the esophagus from extension of the bronchial nodes, but that, too, is unusual. I remember well, however, a woman who had tuberculosis of the spine with involvement of the esophagus that caused definite obstruction.

We should next consider the rare malignant tumors, which conceivably could be a tumor of the lymphoma series. The most frequent type is a reticulum-cell tumor, which occasionally involves the esophagus and could cause this picture. It is extremely unlikely. A history of pain sixteen months before admission, with symptoms for a short period of time and then disappearing, is suggestive of a benign ulcer. A certain number of patients with an ulcer in the lower end of the esophagus have minimal symptoms and may go for a considerable period of time with little difficulty or with symptoms that disappear and recur and that are comparable to those of duodenal ulcer. The question whether or not the dilatation beneath the stricture was stomach in a hiatus hernia cannot be answered by inspection of the films, but since the original examiner mentioned gastric mucosa, I think that it probably was gastric mucosa. We know that there were an ulcer and narrowing, symptoms that are compatible with benign ulcer of the lower end of the esophagus, and I believe that that is the likeliest diagnosis. But I should like to point out that there have been a number of cases of apparently benign ulceration of the lower end of the esophagus that have subsequently proved to have malignant change.

I shall make a diagnosis of benign ulcer of the lower end of the esophagus, with the possibility that it had undergone malignant degeneration.

Dr. Edward B. Benedict: I did the esophagoscopy and found that the margin of the stenosis was smooth. There was little reddening, and I could see no ulcer. The lesion under these circumstances is usually benign, but sometimes malignant disease is found deep down within the stricture.

Dr. Ronald C. Sniffen: Our diagnosis on the biopsy specimen was chronic inflammation. Does that carry any weight with you, Dr. Wallace?

Dr. Wallace: Just as Dr. Benedict has said, one cannot be sure of the diagnosis, just as in prepyloric lesions. Although the x-ray films show an ulcer that appears benign, which is confirmed by esophagoscopy and by examination of the lesion after resection, with careful sectioning in the laboratory, malignant change is often found.

Dr. Benedict: In this case I took specimens from the margin of the stricture and down deep in the stricture so that I believed I had representative sections.

Dr. Wallace: I merely bring that out as a possibility.

DR. RICHARD H. SWEET: I have been much interested in this group of cases, and we now have a small series characterized by the occurrence of a short-esophagus hiatus hernia and inflammatory stricture near the cardia, which in these cases lies well up in the chest.

At exploration in this man we found exactly what we see in the lateral roentgen-ray film, namely, a large portion of the stomach herniated through the diaphragm. The cardia and lower end of the esophagus were thickened. As in all such patients on whom I have operated the area was quite adherent. The adhesions in these cases are different from the ones that are encountered in carcinoma and somewhat more difficult to separate. I believed, as Dr. Wallace did, that this was a benign stricture arising as a result of ulcer in the cardia. This appears to be a definite syndrome. A co-existing duodenal ulcer has been observed in many of the cases. I agree with Dr. Wallace that these lesions should be regarded with suspicion and should be operated on unless it is obvious that they are suitable for dilatation. We have had cases with carcinoma arising apparently in the vicinity of such a stenosed ulcer. A short while ago I had a patient with a similar story, and at operation there was a firm, hard tumor mass, not much larger than 1.5 cm. in diameter, near the fibrous stricture. This led me to be radical in my resection. There was the same kind of stenosed cardia that would appear in a case of fibrosed stricture, but in addition there was a carcinoma, which apparently was extremely early. I know that Dr. Sniffen cannot say that this was a case of carcinoma arising in an ulcer, because of course that is difficult, even in the prepyloric ulcers. At least for the present I should like to think of these lesions in much the same way as we do those in the prepyloric area in the stomach and advise surgery rather than palliative therapy.

DR. BENEDICT: I might say that I have not seen any case with just this setup that had cancer except the one that Dr. Sweet mentioned. I should think that a number of them could be satisfactorily treated by esophagoscopy and dilatation. I am wondering if we ought to do such a radical procedure as partial resection for benign ulcer of the esophagus, except in rare cases.

DR. SWEET: Not unless it is badly stenosed and mechanically obstructed.

DR. BENEDICT: I thought that resection was justifiable in this case, but I am not sure that he could not have been treated with dilatation. We just do not know. A number have been successfully tried. I am inclined to think that the situation is not quite like the prepyloric ulcer, where the danger of malignancy is great.

DR. SWEET: My remarks were intended to direct our thoughts along those lines. I do not believe that we can make a definitive decision but we should keep an open mind. I have a suspicion that we are going to find quite a number of them with carcinoma.

DR. SNIFFEN: One of the major stumbling blocks is that we cannot depend on the biopsy. Frequently, the sections show chronic inflammation and nothing more, and yet there is a cancer. In other words, the biopsy was not taken through a critical area.

CLINICAL DIAGNOSES

Stricture of esophagus, with ulceration and hiatus hernia.

Carcinoma of esophagus?

DR. WALLACE'S DIAGNOSIS

Benign ulcer of esophagus, with stricture.

ANATOMICAL DIAGNOSES

Short esophagus, with inflammatory stricture and ulceration.

Hiatus hernia.

PATHOLOGICAL DISCUSSION

DR. SNIFFEN: Dr. Sweet removed a little more than 2 cm. of the esophagus and a large portion of the part of the stomach that lay above the diaphragm. The upper end of the resected esophagus was dilated to 3.5 cm. in circumference. Below this there was an abrupt narrowing of the lumen, the wall being over 1 cm. in thickness. The stenosis extended for a centimeter or more, ending in the herniated portion of the stomach. In the stenotic area there was a small ulcer, which was not more than 2 mm. in diameter. Histologic sections showed a chronic inflammatory process, with ulceration in the squamous epithelium of the esophagus. There was nothing in the vicinity of the ulcer to lead one to think that there was peptic ulcer of an island of gastric mucosa in the esophagus. We know that these islands may occur anywhere in the esophagus.

I should like to mention the main types of hiatus hernia as enumerated by Harrington.* The first is the true paraesophageal hiatus hernia, in which the termination of the esophagus is below the diaphragm and the fundus has herniated through the esophageal hiatus into the mediastinum. In the second type, the esophagus is again of normal length but the lower end is above the diaphragm. Then there is the group in which the esophagus is congenitally short; he does not consider that this is a true hernia, since the stomach has never been below the diaphragm. Next, there is the acquired short esophagus due to fibrous stricture resulting from tumor or ulcer. I believe that this case falls into that group, except that Dr. Holmes has said that he thought that the process was of short duration. On the other hand, it may have been a congenitally short esophagus with ulceration and stenosis. The last group comprises those cases in which there is dilatation of the lower end of the esophagus without gastric herniation.

*Harrington, S. W. Roentgenologic considerations in diagnosis and treatment of diaphragmatic hernia. *Am. J. Roentgenol.* 49:185-196, 1943.

DR. SWEET: It always seemed to me that it would take a tremendous amount of inflammatory process to produce enough contraction to pull the stomach up from below the diaphragm to a point opposite the pulmonary vein, where this cardia was. It would have to drag the stomach 10 or 12 cm.

DR. SNIFFEN: It is a little difficult to believe.

DR. HOLMES: Instead of stating that the lesion was of short duration, I should have said that the obstruction was of short duration. The esophagus would not dilate unless there was some obstruction.

DR. SWEET: Is not the contraction likely to be circumferential rather than along the length. As we see them they involve short lengths of the esophagus.

DR. BENEDICT: I have seen several cases in which the inflammatory contraction was 10 to 15 cm. long.

DR. SWEET: With a normally placed cardia?

DR. BENEDICT: The cardia was not necessarily abnormally placed.

CASE 31142

PRESENTATION OF CASE

A seventy-two-year-old woman was admitted to the hospital because of inability to swallow solid foods.

Ten months before admission the patient first noticed difficulty in swallowing solid foods. This difficulty gradually became worse, and two months before admission she sought medical advice. She stated that solid food passed part-way down the esophagus, then stopped and was regurgitated. There was no pain. She had lost 25 pounds, had become weak and had experienced a "tight little cough" during the past three to four months. Typical anginal attacks and occasional dyspnea on exertion had occurred during the previous year.

Ten years before entry she had had a radical mastectomy for cancer of the right breast.

Physical examination revealed a well-developed woman who showed evidence of recent weight loss. A right radical mastectomy scar was present; no axillary lymph nodes were felt. Examination of the heart, lungs and abdomen was negative.

The temperature, pulse and respirations were normal. The blood pressure was 154 systolic, 98 diastolic.

Examination of the blood showed a white-cell count of 6100, with 67 per cent neutrophils, and 14 gm. of hemoglobin. The urine was negative. The serum nonprotein nitrogen, the chloride and the protein were normal. A Hinton test was negative. An electrocardiogram suggested some coronary insufficiency.

X-ray examination of the esophagus showed that swallows of barium, both liquid and paste, passed through the esophagus with little delay. The esophagus was seen to be narrowed opposite a tortuous, calcified aortic knob, and a small amount of barium was delayed above this narrowing. Peristalsis of the esophagus was rather feeble. The narrowed area showed normal mucosal folds passing through it. There was no definite filling defect at any point. The lower two thirds of the esophagus showed rather marked curling. A 2-cm. hiatus hernia was noted, which emptied freely. The stomach and duodenum were normal.

On the fifth hospital day esophagoscopy was attempted. The esophagoscope was passed only to the level of the cricopharyngeus muscle, where there was prolonged delay. On gentle pressure some bleeding was noted in that region, and it was thought unwise to attempt to pass the instrument farther. The patient was given nothing by mouth. Intravenous sulfadiazine was started, and x-ray examinations of the neck and chest were performed on the following two days. No evidence of perforation of the esophagus was found. Following the esophagoscopy the temperature rose to 100°F. for a few days. The pulse and respirations remained normal.

On the eighteenth hospital day, as the patient was dressing to go home, she suddenly became dyspneic and cyanotic, broke out with a cold sweat and felt faint but had no pain. She had had no previous similar episode. The lungs were clear, the respiratory rate 30, and the pulse 160, with marked irregularity and pulse deficit. The blood pressure was 180 systolic, 60 diastolic. There was slight distention of the neck veins. She remained cyanotic and dyspneic, and a few hours later became comatose and expired.

DIFFERENTIAL DIAGNOSIS

DR. IRA T. NATHANSON: The initial complaint of difficulty in swallowing focuses attention on lesions in or near the esophagus. Of the benign lesions, the Plummer–Vinson syndrome, scleroderma and vitamin deficiencies must be considered. The first can be ruled out by the absence of the usually long history of dysphagia, the age of the patient, the lack of x-ray evidence of webbing of the esophagus and the relatively normal hemoglobin. The visceral manifestations of scleroderma are less easily eliminated, because of the increased pulmonary markings and the sluggish peristalsis in the esophagus. In the absence of other clinical signs, both these findings may be attributed to the age of the patient. There are no findings recorded to suggest a vitamin deficiency.

One must then consider the malignant lesions that might have been responsible for the clinical picture. Carcinoma of the esophagus may be excluded by the x-ray evidence of normal mucosal folds at the site of narrowing and the absence of a filling defect. Thus, it seems likely that the dysphagia arose from pressure on the esophagus by an extrinsic mass. There are no statements regarding this possibility in the x-ray report. Hence, it would be of help to

review the x-ray films, particularly those of the chest, concerning which nothing is given in the abstract of the history.

DR. LAURENCE L. ROBBINS: The films of the chest show that the right breast had been removed. There appears to be an increase in the linear markings throughout the lung fields beyond what one can expect simply because of the patient's age. There is probably some increase in the density in the anterior portion of the chest; I am not certain what is the cause of this, although it might have been due to an acute process in the left upper lobe, as it appeared within twenty-four hours.

The spot films of the esophagus show it to be fairly smooth in outline; in the lower portion it appears to pass around an extrinsic mass. I do not believe that all the changes can be explained by curling.

DR. NATHANSON: Could the linear markings in the lungs be due to metastases?

DR. ROBBINS: They could be, but they are not typical. The changes could be on the basis of vascular congestion. There is a hiatus hernia.

DR. NATHANSON: If one assumes that an extrinsic mass was the cause of the symptoms, the question arises whether it was primary or secondary. The possibility of a primary mass in the posterior mediastinum cannot be definitely excluded, nor can the exact nature of such a mass be determined. A tumor of the lymphoma series, sarcoid or tuberculous lymph nodes may occur in this region. The latter two are relatively rare at this age, whereas the former may occur at any age. What is the probability of a secondary tumor? The patient had a radical mastectomy ten years previously for cancer of the breast. It is not known if the axillary lymph nodes were involved in disease. It is a well-established fact that metastases from cancer of the breast may remain dormant and not manifest themselves for many years, even twenty-five to thirty, after removal of the primary tumor. Good evidence exists that a five-year follow-up period is not sufficient to evaluate the curability rate of cancer of the breast. Moreover, metastatic lesions from cancer of the breast may appear in a wide variety of locations. The chest is a fairly frequent site. Thus it is possible that there was a metastatic mass in the posterior mediastinum that had its origin from the cancer of the breast removed many years before. Lesions of this character are not necessarily demonstrable by x-ray. There is no evidence of metastatic disease elsewhere. The evidence for this diagnosis is far from conclusive, but I cannot make any other from the material available.

Death can be explained on the basis of coronary disease or a pulmonary embolus.

CLINICAL DIAGNOSIS

Carcinoma of esophagus.

DR. NATHANSON'S DIAGNOSES

(Carcinoma of right breast.)
Metastatic carcinoma of posterior mediastinum.
Hiatus hernia.
Hypertensive and arteriosclerotic heart disease.
Coronary disease?
Pulmonary embolism?

ANATOMICAL DIAGNOSES

(Carcinoma of right breast.)
Radical mastectomy, old.
Metastatic adenocarcinoma of mediastinal lymph nodes, with compression and erosion of esophagus.
Massive pulmonary embolism.
Moderate bilateral hydrothorax.
Fibrinous pericarditis.

PATHOLOGICAL DISCUSSION

DR. RONALD C. SNIFFEN: The patient died from a massive pulmonary embolus, and the inferior vena cava, as well as both femoral veins, contained large thrombi. In the right upper lobe there was a 5-by-3-cm. infarct of a few days' standing.

The mediastinal lymph nodes were matted together and enlarged by obvious tumor deposits. They surrounded the lower trachea and both main bronchi and on the left had produced stenosis of the left upper lobe bronchus, with partial collapse of the upper lobe as a consequence. The bronchial mucosa had been eroded by invading tumor at several points. Posteriorly these same lymph nodes had compressed a 6-cm. segment of the esophagus. The upper margin of compression was at the level of the aortic arch, and 4 cm. below this point the tumor had invaded the anterior wall of the esophagus and produced an erosion measuring 2 cm. in diameter in the mucosa. Additional findings were a moderate bilateral hydrothorax and a fibrinous pericarditis. No tumor could be found at the site of the previous mastectomy or in the other breast.

Microscopically the tumor in the lymph nodes was a poorly differentiated adenocarcinoma having a morphology quite consistent with a metastasis from a breast cancer. The cells lay in a dense collagenous stroma and had a rather striking proclivity for growth in the perineurial lymphatics. The vertebral bone marrow was the only site in which metastatic tumor could be found.

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PENICILLIN: UNEXCELLED AND NOW OBTAINABLE

In a recent poll[1] of a group of leading physicians, penicillin was considered by the majority to be the most valuable drug now used by the medical profession. This recognition was based on two important properties of penicillin, namely, its wide range of effective action in bacterial infections and its lack of significant toxicity for man.

Until a year ago, penicillin could be aptly described as "unexcelled but unobtainable." During the past year the distribution of a limited supply of penicillin through depot hospitals has made it possible for an increasing number of physicians to become familiar with its action from firsthand experience. On March 15 of this year the War Production Board announced that the production of penicillin had increased sufficiently to meet all the anticipated needs of both the armed services and the civilian population and that all restrictions on its sale had been removed. The solution of the difficult problems inherent in the large-scale production of penicillin is a notable accomplishment. Much credit is due the governmental agencies, private scientific institutions, and pharmaceutical manufacturers who have co-operated so effectively to achieve the goal of making the drug available to every patient who might benefit from its administration.

Although there is no reason to anticipate that the unrestricted distribution of penicillin will result in a shortage of the drug, it seems proper to urge physicians to employ this new therapeutic agent with wisdom and discretion. Elsewhere in this issue of the *Journal*[2] the present status of the use of penicillin in the treatment of infections is reviewed in detail. Physicians who have not had an opportunity to use the drug extensively will find this review helpful and timely in acquainting themselves with both the possibilities and limitations of penicillin therapy.

The wider use of penicillin should result in a significant lowering of the mortality rate, a decrease in the number of complications, and a shortening of the period of disability in many of the infections that are commonly encountered in medical practice. It is well to remember, however, that although the drug is nontoxic, it is not a panacea. In certain situations it is conceivable that if blind reliance were placed on the use of penicillin to the neglect of other therapeutic measures of known value, harm might result. Penicillin cannot be expected to have a favorable effect on diseases other than infections caused by organisms that are susceptible to its action, and even in such infections the use of adjuvant measures may often be necessary to effect recovery.

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MEDICAL SERVICE IN INDUSTRY

EVERY vocational association strives to prevent the following of its trade or profession by unauthorized persons. This was begun by the medieval guilds and has been continued and amplified throughout the subsequent history of mankind. The primary purpose and the cause of its great success have always been the enhancement of the political power of its constituents, while they in turn contribute their aggregate strength to the power of the central organization. There is, however, a less well-known but more important purpose — that of protecting the mass of the people against fraudulent and unscrupulous exploitation. Medical-practice laws are framed to support the latter purpose, and it is the solemn obligation of those who make and enforce them to provide the people with a high standard of medical care. It is likewise the obligation of those who are admitted to practice within the law to keep the practice of medicine on a high plane and available to all people at all times.

What legally constitutes the practice of medicine may be a difficult matter to decide. In hospitals and institutions it is frequently necessary that the behavior of those who have to do with the sick and injured be codified into definite procedures. Such methods may be revised or amended from time to time to keep alive and maintain a complete understanding between all concerned. The ultimate responsibility for the choice and execution of the processes of medical care should be assumed by the doctor. In recognition of this responsibility the medical and nursing professions have long since adopted the principles of "doctor's orders"; doctors expect to issue them and to have them carried out, and nurses universally expect to receive them and to carry them out. They have worked well in hospital and private practice because in these surroundings the doctor is expected to assume command; indeed, hospital trustees generally require him to write his orders, where all may see and where there will never be any question about them.

In the development of modern concepts of industrial health, however, there have appeared new relations. Management as a whole cannot be expected to have the same interest or insight into medical care in industry that hospital administrators have in the medical care in their institutions. Industrialists naturally and properly utilize nurses and "first-aiders" to administer immediate aid and to carry out minor treatments. It has sometimes been thought that these nurses and first-aiders were not medically supervised. When, for example, does the giving of an aspirin tablet for a headache constitute medical practice, and when is it a minor commercial or friendly transaction? If the headache is due to meningitis, it is certainly medical practice to treat it in any way — from a first-aid medical cabinet, across a counter or in a hospital; but physicians cannot be expected to examine every case of headache on the remote chance that it may be a symptom of serious disease. Neither can they be expected to ignore everything of a minor nature. There are certain occupations in which headache may be a helpful sign of toxicity and may call for timely and expert medical attention.

All these perplexing and complex relations indicate the need for further clarification of the doctor's role in industry. The Council on Industrial Health of the American Medical Association has advocated standing orders for nurses in industry, and standing orders for industrial first-aiders have been privately issued and used. In its statement elsewhere in this issue of the *Journal*, the Committee on Industrial Health of the Massachusetts Medical Society expresses its approval of standing orders for industrial first-aiders, thus indicating its belief that the supervision of first-aid practices in industry is an obligation of the medical profession. It can be claimed that this is a device under which industrial first-aiders will "practice medicine without a license," and it probably would not be difficult to find cases in which such actually was the case. On the other hand, the practical view, and the one that the committee adopts, is that the first-aider will be less likely to practice medicine if he is forced to work under medical supervision expressed by written standing orders than if he is permitted to proceed independently. This may be a significant step in the protocol of industrial health.

MASSACHUSETTS MEDICAL SOCIETY

COMMITTEE ON INDUSTRIAL HEALTH

The Committee on Industrial Health issues the following statement concerning industrial hygiene in Massachusetts.

DWIGHT O'HARA, *Chairman*

* * *

A STATEMENT CONCERNING INDUSTRIAL HYGIENE IN THE SMALL PLANTS OF MASSACHUSETTS

In two previous reports to the Council of the Massachusetts Medical Society,[1,2] the Committee on Industrial Health has called attention to the fact that three quarters of the workers in Massachusetts are employed in the so-called "small plants" of the Commonwealth, factories where there is still little or no medical supervision of industrial hygiene. The committee has continued to discuss this fact and now ventures to issue a statement about it.

Many of these plants are not so small, — some of them employ 400 or 500 people, which is really a big industry, — but from the point of view of their health standards they are more comparable to the many little industries than they are to those large corporations that have found it feasible and profitable to maintain and staff their own medical departments. In the following discussion the term "small" is therefore used in the sense that it indicates small interest or activity in the field of industrial health.

It is easy to understand why these plants frequently lack this interest. Even though they aggregate a major industrial hazard to the people of Massachusetts, the management of each individual plant can actually concern itself with but a fraction of the total risk. It can insure itself against this fraction and let the matter rest right there. Of course, the chances are that this policy will keep it out of serious trouble, and management naturally is tempted to adopt it and turn its attention to other more pressing matters.

Although this is probably the attitude toward industrial health among many of the small industries, there are today an increasing number of them in which a lively interest in the subject is being shown. When the latter are looked at more closely, it is usually found that an enlightened manager has whipped a doctor into line or an enthusiastic doctor has applied the "bee" to management, or a restless nurse has refused to sink back into the routine of first-aid technics; and so progress has been made. The development of part-time nursing services for industry by district nursing associations was commented on in the report of a year ago[2] and has been described elsewhere.[3] There are many plants in which no nursing service is used, but in which some sort of first-aid equipment has been installed. This is usually presided over by a certified "first-aider" or by someone in the plant who has come to take such responsibilities in the natural course of events. The committee desires to emphasize one point regarding all such persons, from the full-time nurse down to the casual first-aiders, namely, *they need medical supervision.* The complaint that is sometimes heard, or the fear that is sometimes expressed, that some of these people may be "practicing medicine" can mean only one thing — they are not properly supervised by the medical profession.

Such lack of supervision is generally due to one of three kinds of unwillingness: unwillingness on the part of management to employ a plant doctor; unwillingness on the part of the doctor to issue standing orders or to give any advance thought to the health hazards of the particular industry; or unwillingness on the part of first-aid or nursing personnel to refer cases to, or at least to secure advice from, the doctor. A lack of interest and of a sense of responsibility emanating from any one of these three points of view will be an effective barrier to improvement. Positive interest and enthusiasm from all three, on the other hand, will surely raise the standard of industrial health wherever it is applied.

A positive willingness on the part of management to employ a plant doctor must extend beyond the traditional readiness to consult the doctor after something has happened, which is mere medical care. Unless those concerned can look farther ahead and establish standards of prevention and health, they are going to let many things reach the stage of requiring medical care that might well have been stopped in advance. Management should anticipate such things by analyzing its own risks, by utilizing engineering and medical knowledge to eliminate them or to place safeguards about them and by adopting a first-aid policy suitable to the needs of its particular plant. No first-aid policy is adequate if it has not had, in advance, complete medical approval. Management should expect to secure this and to pay for it, and the doctor should expect to provide it and to be paid for it.

A positive willingness on the part of the doctor to be called for purposes of inspection and observation of the conditions under which future patients may be injured, poisoned or exposed is most necessary. Too often — and especially now when all are overworked — the doctor does not believe that he needs to interest himself or to share in the development of such plant policies. He has many other responsibilities, and he naturally allows himself to be distracted by what, at any given moment, most urgently calls for his attention, but the standards of industrial health in the plant that employs him will never be high until he interests himself and assumes his share of the responsibility for the prevention of industrial disease.

The third type of unwillingness, that of the first-aid or nursing personnel to accept supervision of all their activities, is encountered only under special circumstances. Nurses are trained to work under medical supervision at all times, and first-aiders can be made to follow orders readily if the doctor insists on it. In some cases he has to insist on it, for the overconfident type of personality frequently and naturally establishes itself in first-aid positions, and may seek to exploit itself on that basis. It is, however, difficult to understand how any first-aider can overstep his assigned duties if he follows written standing orders from the doctor. On the other hand, when the doctor's interest is not sufficiently forceful, there may develop circumstances under which it may be legitimately charged that someone is practicing medicine without a license.

Chapter 149 of the General Laws of the Commonwealth of Massachusetts (Ter. Ed.), Section 141, states:

> Every person operating a factory, shop or mechanical establishment where machinery is used for any manufacturing or other purpose except for elevators, or for heating or hoisting apparatus, shall keep and maintain, free of expense to the employees, such medical or surgical chest, or both, as shall be required by the department, containing plasters, bandages, absorbent cotton, gauze, and all other necessary medicines, instruments and appliances for the treatment of persons injured or taken ill upon the premises. Every person carrying on a mercantile establishment where twenty or more women or children are employed, shall in the manner aforesaid provide such medical and surgical chest as the department may require.

Under the provisions of this chapter the Department of Labor and Industries requires that a specific list of articles be kept and maintained in a clean and dustproof receptacle. Concerning the use of any of these articles the department provides the simple admonition, "WASH HANDS BEFORE USING." Surely the doctor can improve not only on this standing order but on the inventory of the first-aid kit required by the Department of Labor and Industries.[4]

Standing orders for nurses in industry have been endorsed by the Council on Industrial Health of the American Medical Association,[5] and at least one insurance company has compiled standing orders for industrial first-aiders.[6] The committee expresses its approval of such contacts between the practicing doctor and the industrial nurses and first-aiders. The nature and extent of the contact cannot be sharply delineated, for even in one industry, plants vary, managements vary, nurses vary, first-aiders vary and, above all, doctors vary in their concepts of what medical supervision is to consist. The written standing order, however, constitutes an authoritative level at which responsibility may rest. Although standing orders can often be only a general statement of principles, they are always subject to amendment, modification or alteration by the doctor in charge, and may conveniently provide him with an instrument wherewith he can assert his authority in an impersonal way.

The purpose of this statement is to indicate that progress in industrial health may be expected in the small plants of

Massachusetts by co-operative efforts on the part of managers, doctors, nurses and first-aiders. The absence of such co-operative effort, on the other hand, will effectually block any substantial improvement of the working conditions and environments. This statement is submitted for publication in the *Journal* in the hope that doctors who read it may better visualize their personal opportunities and responsibility in raising the standards of industrial health in the small plants of the Commonwealth.

References

1. Reports of standing committees. *New Eng. J. Med.* **227**:745, 1942.
2. Report of Committee on Industrial Health. *New Eng. J. Med.* **231**: 151, 1944.
3. Wheeler, R. S. Waltham's employee health plan for smaller industries. *Industry* **9**:37-39, 1944.
4. Notice Form 10M-12-41-8080. Department of Labor and Industries, 473 State House, Boston.
5. Council on Industrial Health. Standing orders for nurses in industry. *J. A. M. A.* **122**:1247-1249, 1943.
6. McCoy, D. A., and Zulon, S. S. Suggested standing orders and procedures for industrial first aiders. *Indust. Med.* **13**:689-692, 1944.

DEATHS

BENNETT — William H. Bennett, M.D., of Norwell, died March 5. He was in his seventy-seventh year.

Dr. Bennett received his degree from Baltimore University School of Medicine in 1892. He was a fellow of the American Medical Association. He retired from active practice in 1938.

His widow, a daughter and a granddaughter survive.

KELLEY — Harry N. Kelley, M.D., of Worcester, died February 20. He was in his forty-sixth year.

Dr. Kelley received his degree from Harvard Medical School in 1925. He was on the staff at St. Vincent Hospital. He was a fellow of the American Medical Association.

His widow, a son, a daughter, a brother and two sisters survive.

SANDERSON — Robert Sanderson, M.D., formerly of Dedham, died February 21 in Arlington, Virginia. He was in his forty-second year.

Dr. Sanderson received his degree from Harvard Medical School in 1932. At the time of his death, he was a lieutenant in the medical corps and was stationed at the Navy Department in Washington. He was a fellow of the American Medical Association.

His widow and four children survive.

CORRESPONDENCE

URGENT NEED FOR NAVAL MEDICAL OFFICERS

To the Editor: Because of the constantly increasing demand for naval medical officers, this office has been conducting a minute review of its files in the hope that physicians previously rejected might now be found eligible for a commission. It is therefore evident that for the first time a real opportunity exists for physicians who have been previously disqualified by either the Army or Navy. This action has been precipitated by a communication from Washington in which it was stated that the Bureau wished to review the applications of all doctors wherever there was a possible chance of acceptance. This review includes a large group of rejections based not only on questions of weight, height, color vision, and dental defects, but also such hitherto nonwaiverable conditions as history of healed asymptomatic peptic ulcer, sacroiliac strain, history of asthma and several others. Although waivers will not be promised in such cases, the Bureau definitely wishes to scrutinize each individual case. It is the intention of this office to forward such requests to Washington for reconsideration accompanied by x-ray reports, laboratory data and any other pertinent information which will help to paint an accurate picture of the individual's current condition.

In addition, graduates of unapproved medical schools are encouraged to apply. While the professional examination is still a prerequisite, waivers for nonincapacitating physical defects may be granted to this group as well.

For men who have been declared *essential* by Procurement and Assignment, all we can say is that if a man *really wants to join the Navy*, he may appeal his classification with the assurance that his chances of being reclassified are, in most cases, excellent.

Contrary to public opinion, success in the field does not reduce the need for medical officers. Medical responsibilities mount in direct proportion to the number of victories in the field. The need is not an imaginary one — it rests on a definite factual basis.

This office is in possession of some interesting material that includes the most frequently asked questions regarding doctors and explains the various types of duties to which medical officers are assigned. Interested physicians may obtain copies on request.

H. S. Glidden
Commander MC, U.S.N.R.
Senior Medical Officer

Office of Naval Officer Procurement
150 Causeway Street
Boston 14

DEPRIVATION OF LICENSES

To the Editor: At a meeting of the Board of Registration in Medicine held February 21, the Board voted to revoke the license of Dr. Nathan Gaber, 129 Mt. Vernon Street, Boston, to practice medicine because of gross misconduct in the practice of his profession as shown by collusion.

H. Quimby Gallupe, M.D., *Secretary*
Board of Registration in Medicine

State House
Boston

To the Editor: At a meeting of the Board of Registration in Medicine held March 16, after a re-hearing of the case of Dr. George J. Orlansky, now a captain in the Medical Corps of the Army and formerly of 1234 Blue Hill Avenue, Dorchester, the Board voted to revoke his license to practice medicine in this Commonwealth for not less than three years because of gross misconduct in the practice of his profession as shown by collusion.

H. Quimby Gallupe M.D., *Secretary*
Board of Registration in Medicine

State House
Boston

NOTICES

HARVARD MEDICAL SOCIETY

A meeting of the Harvard Medical Society will be held in the amphitheater of the Peter Bent Brigham Hospital on Tuesday, April 17, at 8:15 p.m. Brigadier Hugh Cairns, Nuffield Professor of Surgery, Oxford University, will speak on the subject "The Use of Penicillin in the Treatment of Pneumococcus Meningitis."

GREATER BOSTON MEDICAL SOCIETY

The next meeting of the Greater Boston Medical Society will be held in the auditorium of the Beth Israel Hospital, Boston, on Wednesday, April 18, at 8:15 p. m. Dr. Fuller Albright will speak on the subject "Osteomalacia." Discussion by Drs. Joseph Aub, Siegfried G. Thannhauser and Sidney Farber will follow.

SOUTH END MEDICAL CLUB

A regular meeting of the South End Medical Club will be held at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston, on Tuesday, April 17, at twelve noon. Dr. William T. Salter, professor of pharmacology, Yale University School of Medicine, will speak on the topic "The Measurement and Adjustment of Endocrine Function."

Physicians are cordially invited to attend.

(*Notices continued on page xvii*)

NOTICES (*Continued from page 414*)

SOCIETY MEETINGS AND CONFERENCES

Calendar of Boston District for the Week Beginning Thursday, April 12

Friday, April 13

*9:00–10:00 a.m. The Diagnosis of Infections Due to Filterable Viruses. Dr. C. A. Janeway. Joseph H. Pratt Diagnostic Hospital.

*9:00–10:00 a.m. Medical clinic. Isolation Amphitheater, Children's Hospital.

10:50 a.m. Common Lesions of the Feet. Dr. Bernard Appel. (Postgraduate clinic in dermatology and syphilology.) Amphitheater, Mallory Building, Boston City Hospital.

12:00 m.–1:00 p. m. Clinicopathological conference (Boston Floating Hospital). Joseph H. Pratt Diagnostic Hospital.

Saturday, April 14

*10:00 a.m.–12:00 m. Medical staff rounds. Peter Bent Brigham Hospital.

Monday, April 16

*12:00 m.–1:00 p.m. Clinicopathological conference. Peter Bent Brigham Hospital.

Tuesday, April 17

*9:00–10:00 a.m. Medical clinic. Infants' Hospital.

*12:15–1:15 p.m. Clinicoroentgenological conference. Peter Bent Brigham Hospital.

Wednesday, April 18

*9:00–10:00 a.m. Penicillin in Venereal Disease. Dr. Oscar F. Cox. Joseph H. Pratt Diagnostic Hospital.

*12:00 m. Clinicopathological conference. Children's Hospital.

*Open to the medical profession.

April 11. Conference on Pan American Affairs. Hotel Statler, Boston.

April 11. Tufts Medical Alumni Association. Page 364, issue of March 22.

April 11. New England Dermatological Society. Page 364, issue of March 22.

April 12. Progress in Dermatology as a Result of World War II. Dr. John G. Downing. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

April 16. New England Heart Association. Page 388, issue of March 29.

April 17. Harvard Medical Society. Page 414.

April 17. South End Medical Club. Page 414.

April 18. Greater Boston Medical Society. Page 414.

April 30. New York Institute of Clinical Oral Pathology. Page 334, issue of March 15.

June 14–19. American Board of Obstetrics and Gynecology. Page 364, issue of March 22.

September 17. American Public Health Association. Page 752, issue of November 30.

District Medical Societies

PLYMOUTH

April 26. Toll House, Whitman.
May 17. Lakeville Sanatorium, Lakeville.
Meetings will be held at 11 a.m.

WORCESTER

April 11. Hahnemann Hospital, Worcester.
May 9. Annual meeting.

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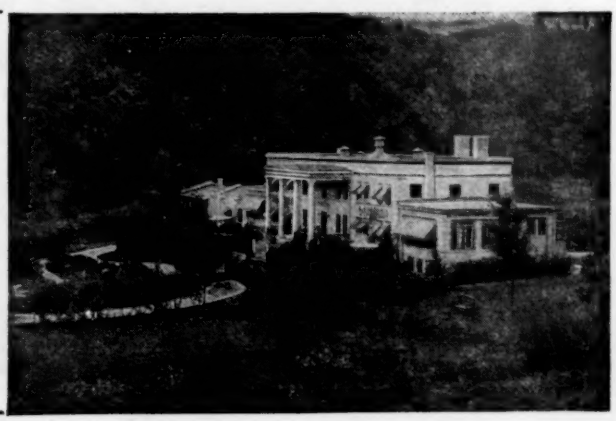

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